IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH) **DEMAND FOR JURY TRIAL**
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC., Plaintiff/Counter Defendants.	

EXHIBIT 15A

SAREPTA THERAPEUTICS, INC. AND THE UNIVERSITY OF WESTERN AUSTRALIA'S MOTION *IN LIMINE* NO. 1 TO EXCLUDE EVIDENCE OR ARGUMENT REGARDING OTHER PROCEEDINGS INVOLVING PATENTS NOT IN SUIT

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SAREPTA THERAPEUTICS, INC. AND THE UNIVERSITY OF WESTERN AUSTRALIA'S MOTION *IN LIMINE* NO. 1 TO EXCLUDE EVIDENCE OR ARGUMENT REGARDING OTHER PROCEEDINGS INVOLVING PATENTS NOT IN SUIT

Sarepta and UWA (collectively, "Counter-Plaintiffs") move under Fed. R. Evid. 402 and 403 to preclude Nippon Shinyaku Co., Ltd. and NS Pharma, Inc. (collectively, "NS") from using evidence of satellite proceedings related to Sarepta and UWA patents other than the patents in suit. The evidence NS wants to use includes prosecution histories of patent applications that are not related to the patents-in-suit, including U.S. Patent Applications (a) 14/743,856, 14/213,641, and 14/776,533 and their child applications ("Species Cases"), and (b) 12/605,275 and its child applications ("Sazani Cases"). These prosecution histories involve unrelated patents with different priority dates and claims of different scope, and they are not asserted as prior art to the Wilton patents. Counter-Plaintiffs also move to preclude NS from using evidence from Interference No. 106,007 (the "'007 Interference") before the U.S. Patent Trial and Appeal Board ("PTAB"), which involved claims of dramatically different scope and a different procedural posture. There is a strong likelihood that the jury would be confused and give undue deference to these satellite proceedings.

In contrast, Sarepta relies on prior proceedings of a different nature. First, for purposes of defending against NS's claim of willfulness, Sarepta relies on its opposition to the European counterpart of the NS Patents asserted in this case, which has claims of *substantially the same scope*. For the same purpose, Sarepta relies on previously-instituted *inter partes* review proceedings for the *NS Patents asserted in this case*. Second, Sarepta and UWA rely on technical declarations submitted during an opposition proceeding for the European counterpart to the Wilton Patents asserted in this case. NS's Dr. Hastings acknowledges that this European patent was "directed to similar subject matter as the '851 Patent" asserted in this case. D.I. 427-5 at ¶ 88. But proceedings involving unrelated patent applications with different priority dates, different

procedural rules, and/or claims of vastly different scope should be excluded as irrelevant and to minimize risk of juror confusion.

I. Proceedings Involving the Species Cases and the Sazani Cases Should Be Excluded Under Rules 402 and 403

The Species Cases and the Sazani Cases do not share the same priority claim as the asserted Wilton Patents and involve different claimed subject matter. Thus, prosecution histories and judicial proceedings related to these cases are irrelevant because they are unrelated to the patents-in-suit. *Sonos, Inc. v. D&M Holdings Inc.*, No. CV 14-1330-WCB, 2017 WL 5633204, at *1 (D. Del. Nov. 21, 2017). Their reference would prejudice Counter-Plaintiffs and be of no probative value. *Id*. These proceedings involving patents unrelated to the patent-in-suit also are "potentially confusing to the jury." *Id*. Because the patents involved in these proceedings are not at issue, any possible probative value is outweighed by the time and confusion that would be involved. *Oracle Am., Inc. v. Google Inc.*, No. C 10–03561 WHA, 2012 WL 1189898, at *3 (N.D. Cal. Jan. 4, 2012) (granting motion *in limine* to exclude information regarding the reexamination of patents not in suit).

In *Plexxikon Inc. v. Novartis Pharmaceuticals Corporation*, the court precluded the patentee from introducing into evidence unrelated patents, finding that "evidence of unrelated patents is likely to cause confusion and waste time as the parties dispute the comparability of those patents, and is thus excluded under Federal Rule of Evidence 403." No. 17-CV-04405-HSG, 2021 WL 2224267, at *2 (N.D. Cal. June 2, 2021).

Additionally, the admission of evidence regarding the prosecution history of different patents would "wast[e] the limited time of the parties explaining the satellite patent prosecutions." *Solvay, S.A. v. Honeywell Specialty Materials LLC*, Civ. No. 06-557-SLR, D.I. 329, slip op. at 2 (D. Del. Sept. 13, 2011) (Ex. A). Allowing arguments or evidence relating to satellite proceedings

involving the Species Cases or the Sazani Cases would require an explanation of the nature of the distinct issues at play including the different priority dates to avoid jury confusion on invalidity issues. As the *Solvay* court explained, "the marginal relevance of the evidence is far outweighed by the danger of unfair prejudice, confusion of the issues, misleading the jury and wasting the limited time of the parties." *Id*.

II. Interference No. 106,007 Should Be Excluded Under Rule 403

Although the '007 Interference involved a patent from the same family as the Wilton Patents, the statements from that proceeding were made in the context of claims that are substantially different in scope and/or in the context of explaining invalidity of a different patent application with a different disclosure. In particular, NS would like to rely on statements from the '007 Interference that were made about a patent application unrelated to the UWA Patents, with a different specification, and filed *before* the UWA Patents. Allowing NS to rely on statements from this proceeding would lead to jury confusion and mislead the jury to believe that these statements also apply to the Wilton Patents.

Courts routinely limit evidence that could confuse or mislead the jury about factual issues. *See, e.g., Oracle*, 2012 WL 1189898, at *3 (granting motion *in limine* to exclude information regarding the reexamination of patents not in suit). Similar to the Species Cases and Sazani Cases, allowing arguments or evidence relating to the '007 Interference would require an explanation of the nature of interference proceedings, the differing standards of proof, and the distinct patents and issues at play, which would "wast[e] the limited time of the parties." *Solvay*, slip op. at 2.

Thus, the Court should exclude any evidence or arguments relating to satellite proceedings involving the Species or Sazani Cases or the '007 Interference under Fed. R. Evid. 402 and 403.

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April 19, 2024

CERTIFICATION PURSUANT TO LOCAL RULE 7.1.1

Defendant and Counter-Plaintiffs Sarepta Therapeutics Inc. and the University of Western Australia certify that a reasonable effort has been made to reach agreement with Plaintiff and Counter-Defendants Nippon Shinyaku Co., Ltd. and NS Pharma, Inc. regarding Counter-Plaintiffs' Motion *in Limine* No. 1. The Parties were unable to reach agreement, and Counter-Defendants refused to agree to Counter-Plaintiffs' requested relief.

/s/ Megan E. Dellinger

Megan E. Dellinger (#5739)

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH)
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC. Plaintiff/Counter-Defendants.	

[PROPOSED] ORDER GRANTING SAREPTA THERAPEUTICS, INC. AND THE UNIVERSITY OF WESTERN AUSTRALIA'S MOTION *IN LIMINE* NO. 1 TO EXCLUDE EVIDENCE OR ARGUMENT REGARDING OTHER PROCEEDINGS INVOLVING PATENTS NOT IN SUIT

At Wilmington this _____ day of _____, 2024, having considered Defendant and Counter-Plaintiffs Sarepta Therapeutics, Inc. and the University of Western Australia's Motion *in Limine* No. 1 to Exclude Evidence or Argument Regarding Other Proceedings Involving Patents Not in Suit, and all papers and arguments submitted therewith, IT IS ORDERED that the motion is GRANTED. Plaintiff and Counter-Defendants Nippon Shinyaku Co., Ltd. and NS Pharma, Inc. are precluded from using evidence of satellite proceedings related to U.S. Patent Applications 14/743,856, 14/213,641, and 14/776,533 and their child applications; U.S. Patent Application 12/605,275 and its child applications; and Interference No. 106,007.

_____
United States District Judge

CERTIFICATE OF SERVICE

I hereby certify that on April 19, 2024, copies of the foregoing were caused to be served upon the following in the manner indicated:

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EXHIBIT A

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

SOLVAY, S.A.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civ. No. 06-557-SLR
	)	
HONEYWELL SPECIALTY MATERIALS LLC and HONEYWELL INTERNATIONAL INC.,	)	
	)	
Defendants.	)	

MEMORANDUM ORDER

At Wilmington this 13th day of September, 2011, having considered the issues raised by Solvay, S.A. ("Solvay") and Honeywell International Inc. ("Honeywell") during the September 8, 2011 pretrial conference, and having reviewed the recent submissions by Honeywell (D.I. 317; D.I. 322; D.I. 327);

IT IS ORDERED that:

1. **The '839 patent and the '309 application.** There are cross motions *in limine* to exclude certain characterizations of Honeywell's '192 patent made in satellite patent prosecutions. The '192 patent is prior art to Solvay's '817 patent.

a. During prosecution of Honeywell's '839 patent, a patent that is not related to any patent in this case, the prosecuting attorney made statements to the PTO as to what the '192 patent disclosed. The patent issued but, subsequently, Honeywell disclaimed the statements and ceded the patent.

b. During prosecution of Solvay's '309 application, a related application to

the '817 patent, the patent examiner rejected claim 19 (substantially identical to claim 1 of the '817) on the basis that the '192 patent disclosed a continuous process. Solvay subsequently abandoned the application.

c. In both instances, the marginal relevance of the evidence is far outweighed by the danger of unfair prejudice, confusion of the issues, misleading the jury and wasting the limited time of the parties explaining the satellite patent prosecutions. Therefore, neither the '839 patent evidence nor the '309 application evidence shall be admitted.

2. **Priority date.** A priority date of October 23, 1995 has been established. Honeywell conceded that it did not intend to rely on any evidence or any reference in the expert reports or the late-produced documents which would affect the priority date. (9/8/11 Tr. at 34:4-7) The court sees no reason to reopen the issue of the priority date at this time when it admittedly has no bearing on the merits of the case.

3. **Dependent claims.** The court concludes that independent claim 1 is the only clam that shall be submitted to the jury. Dependent claim 11 was never explicitly discussed in Solvay's expert report, and the jury would be required to infer the relevance of the expert's statements as to claim 11.

4. **Expert witness statement on the Russian '430 patent.** The court shall grant Honeywell's motion for leave to serve an expert witness statement on the disclosure of the Russian '430 patent, one of the late disclosed documents that has become a critical issue in the case since the Federal Circuit's decision. (D.I. 317) Specifically, the court shall permit both parties' expert witnesses to supplement their

reports on the limited issue of what is disclosed by the Russian '430 patent. The parties shall exchange the reports within five days of the entry of this order. The parties shall be permitted to conduct a two-hour deposition of the opposing expert limited to the contents of the supplemental reports.

5. **Motions for reargument.** The court denies Honeywell's motions for reargument. (D.I. 322; D.I. 327) By way of its first motion (D.I. 322), Honeywell contends that the court's August 26, 2011 opinion (D.I. 299) regarding the issue of abandonment, suppression or concealment is inconsistent with the court's December 9, 2008 opinion (D.I. 230) regarding the same issue, in which the court granted summary judgment of invalidity in favor of Honeywell. According to Honeywell, the contractual relationship between the RSCAC and Honeywell and Honeywell's ownership of the RSCAC's invention under that agreement enables the RSCAC to make disclosures through Honeywell in a manner sufficient to preclude a finding of abandonment, suppression or concealment by the RSCAC. (D.I. 322) Although the Federal Circuit did not disturb this court's conclusion regarding abandonment, suppression or concealment in its December 8, 2009 decision, the Federal Circuit's ruling indicates that Honeywell's actions and the actions of the RSCAC are not interchangeable in identifying "another inventor."[1] The plain language of § 102(g)(2) supports the same rationale with respect to the abandonment, concealment or suppression inquiry: "[B]efore such person's

[1]"Honeywell is not 'another inventor' under § 102(g)(2). That is clear from the facts set forth above, which are undisputed. As noted, working pursuant to RSCAC's research contract with Honeywell, Russian engineers conceived of the process for making HFC-245fa in Russia." *Solvay S.A. v. Honeywell Int'l, Inc.*, 622 F.3d 1367, 1377 (Fed. Cir. 2010).

invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it," indicating that the "another inventor" (in this case, the RSCAC) must disclose the invention. 35 U.S.C. § 102(g)(2). Therefore, the inquiry is whether the RSCAC, not Honeywell, disclosed the invention.

6. By way of its second motion for reargument (D.I. 327), Honeywell contends that the court relied on Solvay's misapplication of the Federal Circuit's holding in *Dow Chemical Co. v. Astro-Valcour, Inc.*, 267 F.3d 1334 (Fed. Cir. 2001) in deciding to exclude evidence of the '706 patent.[2] (D.I. 327) Honeywell relies on *Dow Chemical* and *Checkpoint System, Inc. v. U.S. International Trade Commission*, 54 F.3d 756 (Fed. Cir. 1995), for the proposition that a prior invention by an employee is not abandoned, suppressed or concealed due to the public disclosure of the invention by the employer. However, Honeywell and the RSCAC did not maintain an employer / employee relationship and, as described in the previous paragraph, the Federal Circuit made clear that Honeywell's actions and the actions of the RSCAC are not interchangeable for purposes of § 102(g).

7. **Inequitable conduct.** Having reviewed Honeywell's statement of intended proof regarding Solvay's inequitable conduct during prosecution of the '817 patent (D.I. 324), the court concludes that Honeywell has failed to meet its threshold burden set forth in *Therasense, Inc. v. Becton, Dickinson & Co.*, _____ F.3d _____, 2011 WL

[2]The court acknowledges that the Federal Circuit in *Dow* affirmed the district court's opinion and did not "revers[e the] district court's holding" of no abandonment, suppression or concealment. However, the Federal Circuit found that "the district court erred in its finding that the AVI could not have abandoned, suppressed, or concealed the invention because it had previously become publicly known when the Miyamoto patent issued in 1974." *Dow Chem.*, 267 F.3d at 1342.

2028255 (Fed. Cir. May 25, 2011), to establish a cause of action for inequitable conduct. "To prevail on the defense of inequitable conduct, the accused infringer must prove that the applicant misrepresented or omitted material information with the specific intent to deceive the PTO. The accused infringer must prove both elements – intent and materiality – by clear and convincing evidence." *Therasense*, 2011 WL 2028255, at *6. Specifically, "the accused infringer must prove by clear and convincing evidence that the applicant knew of the reference, knew that it was material, and made a deliberate decision to withhold it." *Id.* at *9. The evidence proffered by Honeywell does not establish the requisite level of intent by Solvay to establish inequitable conduct by clear and convincing evidence.

8. **Equitable estoppel.** The court shall hear the parties on the issue of equitable estoppel in a bench trial to be scheduled subsequent to the jury trial.

United States District Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH) **DEMAND FOR JURY TRIAL**
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PLAINTIFF'S RESPONSE TO SAREPTA THERAPEUTICS, INC. AND THE UNIVERSITY OF WESTERN AUSTRALIA'S MOTION *IN LIMINE* NO. 1 TO EXCLUDE EVIDENCE OR ARGUMENT REGARDING OTHER PROCEEDINGS INVOLVING PATENTS NOT IN SUIT

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Dated: April 25, 2024

Sarepta and UWA spent years seeking claims directed to exon 53-skipping antisense oligonucleotides ("ASOs"). Before the PTO, they factually represented that the relevant art remained "highly unpredictable" long after June 28, 2005 (the UWA Patents' earliest possible filing date). Sarepta has likewise argued that Popplewell's exon 53 research teaches away from claims covering its product VYONDYS 53® (golodirsen). And yet, Sarepta will argue the ***opposite*** to the jury—that its asserted UWA patents "resolved the unpredictability" with exon 53 skipping in 2005, (*e.g.*, D.I. 469 at 21), and that an ASO targeting positions 36 to 60 is obvious.

Sarepta's and UWA's motion improperly seeks to shield themselves from the natural consequences of their sudden about-faces. Sarepta suggests that NS will ask the jury to "give undue deference" to the rulings in "satellite proceedings." MIL Mot. at 1. Not so. NS plans to highlight material ***factual admissions*** Sarepta and UWA made to the Patent Office. Precluding NS from raising party admissions on critical issues and fairly impeaching Sarepta's and UWA's credibility would be erroneous and unfairly prejudice NS. The Court should deny this motion.

I. Sarepta/UWA Relied Upon the '007 Interference to Obtain the Asserted Patents

The '007 Interference involved exon 53-skipping ASOs, a UWA patent family member and an earlier-priority application from Academisch Ziekenhuis Leiden ("AZL"). Sarepta (who controls the UWA patents) explicitly asserted that the field of exon skipping was—and ***in 2014 continued to be***—"highly unpredictable." Ex. 1, (UWA Mot. 1) at 17 (brief dated Nov. 18, 2014) ("Exon skipping of dystrophin pre-mRNA was a nascent and highly unpredictable technology as of the time of the invention (***and remains so today***).").[1] According to Sarepta, not only was "the path to identifying other[exon 53-skipping ASOs] was largely unknown" "[w]hen the competing applications in this interference were filed," but also their "***[s]ubsequent experience*** has revealed

[1] All emphases added unless otherwise stated.

that operative sequences ***are actually highly unpredictable***." Ex. 1 (UWA Mot. 1) at 1.

After persuading the PTAB to adopt these facts in the '007 Interference, Ex. 2 (PTAB Decision (May 12, 2016)) at 11-17, Sarepta (1) repeated them in prosecuting the asserted '851 Patent (parent to the '590 and '827 Patents); and (2) urged the Examiner to adopt them, Ex. 3 (D.I. 428-6) at 4790-95 (arguing the PTAB "held that the field . . . was unpredictable"). In a 2018 Office Action response, Sarepta swore that exon skipping "***remains*** an unpredictable exercise," (*id.* at 4794), and "recognition of the lack of predictability in the field of exon skipping ***continued beyond 2005***," (*id.* at 4793). Again, Sarepta convinced the PTO these facts were true and secured issuance of the now-asserted claims. *Id.* at 4947 (citing "Applicant's argument" regarding motivation).

Put simply, the '007 Interference admissions are relevant and "intrinsic" evidence to the asserted UWA Patents on the art's unpredictability. Sarepta's specific reliance on the '007 Interference to prove unpredictability and secure the now-asserted claims further highlights their critical relevance. That the claimed subject matter in the '007 Interference and Sarepta's/UWA's asserted claims substantially overlaps each other also supports their admissibility.[2]

II. Sarepta Made Relevant Factual Admissions in the "Species" and "Sazani Cases"

NS seeks to admit targeted factual admissions from the "Species" and "Sazani Cases." In prosecuting Appl. No. 14/776,533, Sarepta contradicted its current obviousness contention. Sarepta's obviousness theory for the NS Patents uses hindsight to select a 25-mer ASO ("PMO-A") tested by Popplewell and modify it to reach the claimed 25-mer PMO (targeting positions +36+60 in exon 53, and a 5' TEG moiety). Ex. 5, Dowdy Op. Rpt. ¶ 462. Sarepta's '533 Application sought to claim that 25-mer PMO, but was rejected over Popplewell's research. Ex.

[2] The Examiner's obviousness rejection for the '851 Patent asserted the same ASO (h53AON1, SEQ ID No. 29) around which AZL based its genus. *Compare* Ex. 4, (D.I. 428-5) at 4609-4610 (SEQ ID No. 195 "overlaps with 3 nucleotides"), *with* Ex. 1 (UWA Mot. 1) at 12 (cls. 78 and 100).

6, Hastings Resp. ¶ 192. According to Sarepta then, Popplewell's PMO-A "produced little to no skipping," a POSA would choose "one of the more active compounds," and "Popplewell teaches away from" 25-mer PMOs and "shortening the 30-mer." *Id.* ¶¶ 193-94, 195. And "changing [an ASO's] target coordinates" "in either the 5' or 3' direction is not predictable." *Id.* ¶ 199.

NS's other reliance on "Species" and "Sazani" cases is also targeted to precise issues. Sarepta contends that a "Sazani 2010" article was non-cumulative of other references NS disclosed to the Patent Office, but Sarepta itself did not disclose that article when it sought to claim the same subject matter in the '533 Application. Ex. 6, Hastings Resp. ¶¶ 255, 261-64. Other "Species Cases" rebut Dr. Dowdy's reliance on their disclosures as post-priority date evidence supposedly confirming UWA's "hot spot." Ex. 7, Hastings Rep. ¶ 58. Dr. Hastings points out in reply that, in prosecuting "Species Cases" directed to NS's accused VILTEPSO® product—which Sarepta contends the UWA Patents' claimed genus encompasses—Sarepta argued that UWA's later work "does not teach all of the elements" of that (allegedly infringing) ASO.[3] *Id.* ¶¶ 59-64.

* * *

Sarepta's authority does not support its request. *Oracle* allowed the asserted patents' reexamination and "specific item[s]" from others. *Oracle Am., Inc. v. Google Inc.*, 2012 WL 1189898, at *3 (N.D. Cal. Jan. 4, 2012). *Plexxikon* allowed "prior inconsistent statements." *Plexxikon Inc. v. Novartis Pharms. Corp.*, 2021 WL 2224267, at *2 (N.D. Cal. June 2, 2021). And *Solvay* involved fact-specific rulings. *Solvay, S.A. v. Honeywell Specialty Materials LLC*, Civ. No. 06-557-SLR, D.I. 329, slip op. at 2 (D. Del. Sept. 13, 2011) (Ex. A). Yet, the law is clear that patentees' prosecution admissions are "binding" and should be "accepted at face value." *Procter & Gamble Co. v. Nabisco Brands, Inc.*, 711 F. Supp. 759, 770 (D. Del. 1989); D.I. 400 at 7.

[3] If the Court precludes reliance on post-priority date evidence to support validity, NS would not need to introduce this particular evidence.

Dated: April 25, 2024

Respectfully submitted,

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Exhibit 1 to NS's Response to Sarepta's MIL No. 1

Filed on behalf of: Junior Party **UNIVERSITY OF WESTERN AUSTRALIA**

Paper No. _____

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Date Filed: November 18, 2014

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT TRIAL AND APPEAL BOARD

University of Western Australia,
Junior Party
(Patent 8,455,636,
Inventors: Stephen Donald Wilton, Sue Fletcher and Graham McClorey)

V.

Academisch Ziekenhuis Leiden,
Senior Party
(Application 11/233,495
Inventors: Garrit-Jan Boudewijn van Ommen, Judith Christina Theodora van Deutekom, Johannes Theodorus den Dunnen and Annemieke Aartsma-Rus).

Patent Interference No. 106,007 (RES)
(Technology Center 1600)

UNIVERSITY OF WESTERN AUSTRALIA MOTION 1
(For Judgment Under 35 U.S.C. § 112(a))

I. Precise Relief Requested

Pursuant to 37 C.F.R. § 41.121(a)(1)(iii), the University of Western Australia ("UWA") requests entry of judgment that Academisch Ziekenhuis Leiden's ("AZL") Application No. 11/233,495 ("the '495 application") fails to provide adequate written description support for, and/or fails to enable, AZL's involved claims as required by 35 U.S.C. § 112(a).

II. Evidence in Support of the Motion

Appendix 1 is a list of exhibits cited in support of this motion. The requirement for a statement of material facts has been waived. (*See* Paper 19 at 5.)

III. Summary of the Argument

When the competing applications in this interference were filed, a handful of specific operative exon skipping antisense oligonucleotides ("AONs") targeting exon 53 had been discovered, and the path to identifying others was largely unknown. Both parties submitted broad generic claims in the hope that identification of broader families of operative AONs would follow predictably from those narrower discoveries. Subsequent experience has revealed that operative sequences are actually highly unpredictable, varying with parameters such as nucleobase sequence, length, backbone chemistry, and internucleotide linkages. Experience with exon skipping is consistent with the now familiar challenges with antisense technology generally. *See, e.g.*, *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1372 (Fed. Cir. 1999) ("[A]ntisense strategies have not been as universally straightforward or as easy to apply as was initially hoped . . . .") Accordingly, UWA brings this motion challenging the patentability for the full breadth of AZL's claims under the written description and enablement requirements.

The involved claims of AZL's '495 application are directed to AONs capable of inducing the cellular splicing machinery to "skip" exon 53 of the dystrophin gene during processing of the dystrophin pre-mRNA. At the filing date of the '495 application, exon skipping was very much

number of combinations, because the claim is open to ***any*** possible chemical modification to the chemical backbone and to the internucleotide linkages, provided that the AON contains a single modification from the recited list. (Exh. 2081 at ¶ 196.) Thus, the immense breadth of these claims is derived from (1) the varying ranges of possible AON length; (2) the immense number of possible nucleobase sequence combinations; (3) the potential for an unspecified number of "mismatches" with the target sequence; (4) the immense number of possible chemical backbone and internucleotide linkage combinations; (5) the possibility of non-natural bases; and (6) the potential for other chemical modifications.

Independent claims 78 and 100 are "capable of binding" claims, and if anything are even broader. They state as follows:

> 78. An isolated antisense oligonucleotide of 18 to 50 nucleotides in length, wherein said oligonucleotide is capable of binding to an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA and inducing skipping of exon 53, and wherein h53AON1 (cuguugccuccgguucug) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-*O*–methyl, 2'-*O*-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a modification to increase resistance to RNAseH, a peptide nucleic acid and a locked nucleic acid.
>
> 100. An isolated antisense oligonucleotide of 18 to 50 nucleotides in length, wherein said oligonucleotide is complementary to a consecutive part of between 16 and 50 nucleotides of an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA and is capable of inducing skipping of exon 53, and wherein h53AON1 (cuguugccuccgguucug) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA, said oligonucleotide comprising a modification selected from the group consisting of: 2'-O –methyl, 2'-O-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a modification to increase resistance to RNAseH, a peptide nucleic acid and a locked nucleic acid.

(Exh. 2045 at 1-3.)

Neither of these claims recites *any* particular nucleobase sequence that must be included within the claimed AON. (Exh. 2081 at ¶ 208.) Instead, claim 78 requires that the claimed AON

1. The '495 Application Does Not Disclose Species that Are Representative of the Broad Genera Defined by the Independent Claims

The '495 application discloses only a single AON purportedly capable of inducing *in vitro* skipping of exon 53. (Exh. 2041 at 15, Table 2; Exh. 2081 at ¶ 278.) That single species fails to adequately support AZL's broad genus claims.

Exon skipping of dystrophin pre-mRNA was a nascent and highly unpredictable technology as of the time of the invention (and remains so today), as demonstrated by publications from investigators in the field (Exh. 2015 at 8; Exh. 2017 at 644), publications by the AZL applicants (Exh. 2012 at 1548; Exh. 2013 at 807; Exh. 2014 at 548; Exh. 2018 at 911; Exh. 2020 at 259-60; Exh. 2024 at 238; Exh. 2025 at 450), AZL's submissions to other patent offices (Exh. 2042 at 29, 49; Exh. 2085 at 1; Exh. 2084 at 3), and the disclosure of the '495 application itself (Exh. 2041 at [0051], Table 2). Given this unpredictability, a skilled person would need to empirically determine whether any given AON encompassed by claims 15, 76, 78, or 100 would be capable of inducing skipping of exon 53. (Exh. 2081 at ¶¶ 280-326.)

Disclosure of h53AON1 is insufficient to provide a description of the full scope of AZL's independent claims. *E.g. In re Curtis*, 354 F.3d at 1358 (disclosure of a single species within a claimed genus will not convey possession of the genus when evidence indicates that ordinary artisans could not predict the operability in the invention of any species other than the one disclosed); *Eli Lilly*, 119 F.3d at 1568 ("A description of rat insulin cDNA is not a description of the broad classes of vertebrate or mammalian insulin cDNA."); *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014) ("Functionally defined genus claims can be inherently vulnerable to invalidity challenge for lack of written description support, especially in technology fields that are highly unpredictable, where it is difficult to establish a correlation between structure and function for the whole genus or to predict what

Respectfully submitted,

Dated: November 18, 2014

By: By: */s/ R. Danny Huntington*

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Exhibit 2 to NS's Response to Sarepta's MIL No. 1

BoxInterferences@uspto.gov Entered: May 12, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT TRIAL AND APPEAL BOARD

University of Western Australia,
Junior Party
(Patent 8,455,636,
Inventors: Stephen Donald Wilton, Sue Fletcher and Graham McClorey),

v.

Academisch Ziekenhuis Leiden,
Senior Party
(Application 11/233,495,
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Patent Interference No. 106,007 (RES)
(Technology Center 1600)

Before: RICHARD E. SCHAFER, SALLY GARDNER LANE, and DEBORAH KATZ, *Administrative Patent Judges*

SCHAFER, *Administrative Patent Judge.*

Decision - Motions - 37 CFR § 41.125(a) (Substitute)

This interference is between University of Western Australia (UWA) Patent 8,455,636 and Academisch Ziekenhuis Leiden (AZL) Application 11/233,495.

Paper 210, 4:8-10. As a result, according to UWA, each proposed AON must be empirically tested to verify its ability to cause exon skipping. UWA Motion 1, Paper 210, 4:11-13. Because of this unpredictability, UWA argues, AZL's single disclosed operative species within the scope of AZL's claims—the AON designated h53AON1—is insufficient to support the genus of exon 53-skipping AONs encompassed by UZL's claims. UWA Motion 1, Paper 210, 15:18 – 16. In other words UWA argues that from the disclosure of (1) h53AON1, (2) its ability to cause exon 53 skipping, and (3) the rest of the '495 application disclosure, one skilled in the art would not conclude that UZL's inventors had possession of the broad genus of AONs said to be encompassed by AZL's claims.

AZL responds that each of the limitations of its claims is expressly found in its written description. AZL Opposition 1, Paper 392, 6:21 – 7:7. AZL also argues that antisense technology is a mature and predictable field for which AONs are a fundamental tool and that the AON art is sufficiently predictable that the disclosure of the single species h53AON1 in the form a sequence listing provides adequate written descriptive support for the genus claimed. AZL Opposition 1, Paper 392, 2:7-10.

4.

To establish that those skilled in the art considered exon skipping to be unpredictable, UWA relies on the testimony of Dr. Wood. He testifies that exon skipping is unpredictable. Ex. 2081, ¶ 68. In support of his testimony, he identifies a number of publications covering the period 2001 – 2011, a period beginning before and extending after AZL's September 21, 2005, filing date. We summarize some of these publication below.

A 2001 peer-reviewed publication relating to exon 46 skipping titled "Antisense-induced exon skipping restores dystrophin expression in DMD patient

derived muscle cells" (Ex. 2012) indicates that it is difficult to predict the AONs that will bind to the target exon:

> The efficacy of AONs is largely determined by their binding affinity for the target sequence. Due to base composition and pre-mRNA secondary or tertiary structure, *it is difficult to predict which AONs are capable of binding the target sequence*.

Ex. 2012, p. 1548 (emphasis added). The authors tested 12 AONs having overlapping sequences for exon binding and skipping of DMD exon 46 in mouse muscle cells (mAONs 1-12). Ex. 2012, p. 1548. The AONs were complementary to portions of exon 46 differing in specific sequences and sequence length. Ex. 2012, p. 1548, Fig 1B. The mAON's were said to be 15 or 20 nucleobases in length. Ex. 2012, p. 1550, Table 1. Only five of the twelve, mAONs 4, 6, 8, 9, and 11, were identified as binding to Exon 46. Ex. 2012, p. 1548-50, Figs. 1B, 2A and Table 1. Four of the mAONs –4, 6, 9 and 11—were said to cause skipping of exon 46. Ex. 2012, p. 1548 and Figs. 2C and 2D. mAON 8, which was said to bind to exon 46 and shared an eleven nucleotide sequence with mAON 9 and a seven nucleotide sequence with mAON 11, did not cause exon skipping. Ex. 2012, p. 1548. mAON 10 which apparently shared partial nucleotide sequences with mAON 9 and 11 (Fig. 1B), was not reported as binding with exon 46. Ex. 2012, p. 1548. Additional experiments were reported with respect to human muscle cells using the human AON versions (hAONs) said to correspond to mAONs 4, 6, 8, 9 and 11. Ex. 2012, p. 1548-49. The human versions (hAONs) were also 15 or 20 nucleotides in length. Ex. 2012, Table 1. With respect to human muscle cells, hAONs 4, 6, 8 and 9 were said to bind, but only 4, 6 and 8 were said to cause skipping. Ex. 2012, p. 1549. hAONs 9 and 11, which share an eleven and seven nucleotide sequences, respectively, with the exon-skipping hAON 8, were not

identified as causing exon skipping. Ex. 2012, p. 1549. All the exon-skipping AONs were 15 or 20 nucleobases in length.

In a 2002 peer-reviewed article titled "Targeted exon skipping as a potential gene correction therapy for Duchenne muscular dystrophy" (Ex. 2010) identified 30 potential AONs for 15 different exons. The authors state that there is no significant correlation between effectiveness and the length or sequence content and that effectiveness of proposed AONs to bind to the desired exon needs to be tested empirically:

> Of the 30 AONs tested, as many as 20 induced specific exon skipping. *There was no significant correlation between the length or sequence content of the AON and its effectiveness (see Table 1)*. We hypothesize that in most cases the mere accessibility of the targeted RNA region, and thus the capability of the AONs to bind, determines their efficacy. The fact that with the AONs tested so far, we have not been able to induce the skipping of exons 45, 47 and 48 would, in this model, be explained by a less accessible configuration of these exons within the secondary structure of the pre-mRNA. To predict the secondary structure of the targeted pre-mRNA regions, we have used the RNA mfold version 3.1 server. Although this analysis hints at the most favorable local structure which may help in the design of AONs, it is not capable of predicting the overall complex structure of the entire DMD pre-mRNA. *We therefore have no insight into the actual position of the targeted sequence within the completely folded RNA structure. Its accessibility, and thus the effectivity of any designed AON, will therefore still have to be tested empirically in the cells, as was done in this study*.

Ex. 2010, p. S76 (emphasis added). The publication appears to rely on much of the same data presented in AZL's involved application. Compare Ex. 2010, Tables 1, 2 and 3 and Figure 1 with AZL's involved application, Ex. 1008, Tables 2, 3 and 4 and Figure 5, respectively. However, unlike AZL's application disclosures, the publication does not make any predictions as to additional AONs that include the

skip-causing sequences, but also include additional exon-complementary nucleobases. All the AONs reported to have successfully caused exon skipping are reported as 15-24 nucleobases in length. Ex. 2010, Table 1.

In another 2002 peer-reviewed publication titled "Improved Antisense Oligonucleotide Induced Exon Skipping in the mdx Mouse Model of Muscular Dystrophy" (Ex. 2017) the authors report making a number of AONs that bound to the region of the dystrophin gene exon 23/intron 23 boundary. Ex. 2017, 646. Three were said to successfully cause skipping. Ex. 2017, p. 631, col. 2. Those AONs were reported to be 17 to 25 nucleobases long.

A 2007 peer-reviewed publication titled "Comparative Analysis of Antisense Oligonucleotide Sequences for Targeted Skipping of Exon 51 During Dystrophin Pre-mRNA Splicing in Human Muscle" (Ex. 2013) notes that rules to assist in determining likely candidates for exon skipping in human and mouse muscle cells *in vitro* had yet to be identified although the sequence length and target region are singled out as important:

> *[S]everal years after the first attempts at dystrophin exon skipping with [AONs], there are still no clear rules to guide investigators in their design, and in mouse and human muscle cells in vitro there is great variability for different targets and exons.* The consensus sequences at the intron–exon boundaries that are involved in splice site selection are only poorly conserved, and the [exonic splicing enhancers] that are involved in exon definition are themselves of multiple motifs and their identification is complex. *Until these key elements are better understood only length and target region seem to be important when designing exon skipping [AONs] for the DMD gene.*

Ex. 2013, p. 807 (citation omitted, emphasis added). The successful AONs tested (A20 and B30) were reported as being 20 and 30 nucleobases in length. Ex. 2013, 803, Table 2.

The 2009 article titled "Guidelines for Antisense Oligonucleotide Design and Insight Into Splice-modulating Mechanisms" (Ex. 2014) notes that notwithstanding the development of various computer programs to assist in identifying AON's as exon skipping candidates, a trial and error procedure was still necessary. The importance of AON sequence length was also noted:

> Each antisense mechanism requires stable and efficient binding of the AON to its target sequence. One obvious determinant of AON efficacy is the accessibility of the target . . . . Several software programs are available to predict the secondary structure of RNA, of which the m-fold server is the most widely used. This server also provides a so-called SS-count for the target sequence, indicating the propensity of a nucleotide to be single stranded in a number of potential secondary structure predictions. This approach probably reflects the actual *in vivo* situation more closely than focusing only on the most energetically stable structure. In addition, the stability and binding energy of the AON to the target sequence influence AON efficiency. *This depends on e.g., AON length and sequence constitution and the free energy of local structures*. To efficiently bind a target sequence, the free energy of the AON-target complex must be higher than that of the target complex and that of the AON. *As AONs are generally only 17–25-nucleotides long, they are unlikely to form stable secondary structures*. However, most AONs can form AON–AON complexes with other AONs of the same sequence (Supplementary Figure S2). The software program RNAstructure 4.5 has a tool that provides the free energy of AON–AON complexes and AON-target complexes, in addition to the free energy of individual AONs and the target sequence. The aforementioned software programs (as well as others) can be used to facilitate AON design (reviewed in ref. 1). *Nonetheless, none of them is 100% conclusive or predictive and in general a trial and error procedure is still involved to identify potent AONs*.

Ex. 2014, p. 548 (emphasis added, citation and footnote omitted).

A 2011 publication titled "Targeted Skipping of Human Dystrophin Exons in Transgenic Mouse Model Systemically for Antisense Drug Development" (Ex. 2015). The authors reported the results of a test using 32 AONs that covered more than two-thirds of human dystrophin exon 50 and its two flanking intron sequences. Ex. 2015, p. 3, paragraph bridging col. 1 and col. 2. The selected AONs had different lengths and were targeted to different portions of exon 50 and its flanking introns. Ex. 2015, Table 1. Thus, all the AONs were antisense to complementary portions of exon 50 and its flanking introns. The results for the 25 AONs with 2OMePS backbones are shown in that publication's Table 1. Ex. 2015, p. 4. Seven of those AONs were identified as causing exon 50 skipping. Review of the Table 1 data shows that the AON length significantly effects exon skipping notwithstanding the inclusion of a common sequence. For example, AONs hE50AO2PS – hE50AO6PS all share the same nineteen base pair sequence. Ex. 2015, Table 1. The 19 and 20 base pair hE50AO2PS and hE50AO3PS were not identified as causing exon skipping. The 22 base pair hE50AO4PS (two additional base pairs) on the 5' end was said to cause skipping in 4% of cells. The 27 base pair hE50AO5PS, with an additional 5 base pairs at the 5' end over hE50AO4PS, was said to cause skipping in 21%. The 32 base pair hE50AO6PS with 5 more base pairs added to the 5' end resulted in 3% notwithstanding that the entire 27 base pair sequence of hE50AO5PS is part of the 32 base pair sequence of hE50AO6PS. We find that this data shows that, given the sequence of an AON capable of causing exon skipping, adding and subtracting additional complementary nucleotides significantly effects the capability of the AON to maintain exon skipping. The data also shows that when an AON's sequence is modified by adding or subtracting a relatively small number of nucleobases, exon skipping is maintained. Compare hE50AO5PS (27 bases) with hE50AO6PS (32

bases) and hE50AO4PS (22 bases). Ex. 2015, Table 1. Additionally, the sequence length of all the exon-skipping AONs fall within the range of 17-32 nucleobases.

The evidence indicates that at the time AZL filed its application, the identification of AONs that will cause exon skipping was generally thought to be unpredictable. One of the significant factors causing that unpredictability is the effect of the number of nucleobases present in the AON.

5.

AZL also argues that once h53AON1 was identified, one skilled in the art would have investigated extended complementary sequences with the expectation that the longer sequences would bind and cause skipping. AZL Opposition 1, Paper 392, 22:2 – 22:9. AZL directs us to Dr. Sontheimer's testimony to support its argument. Dr. Sontheimer testifies that "given the proven exon-skipping ability of h53AON1, one of skill in the art would have a high expectation that such AONs of up to 80 nucleotides in length would bind its target and induce exon skipping." Ex. 1186, ¶ 114, 35:2-5. Dr. Sontheimer does not direct us to any evidence or provide an explanation why one skilled in the art would have had a high expectation. We are not required to credit the unsupported opinions of an expert witness. *Rohm and Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997).

AZL argues that in considering the permissible scope of genus claims with respect to § 112, the consideration is "the predictability of the aspect at issue." AZL Opposition 1, Paper 392, 20:2 – 22:9. AZL cites to *Capon*, 418 F.3d at 1359. AZL argues that none of the publications cited by UWA pertain to the predictability of the "aspect at issue." The aspect at issue is said to be AONs having a sequence capable of binding to and causing skipping of exon 53. AZL Opposition 1, Paper 392, 21: 6-10. According, to AZL the "aspect at issue" is specifically tied to exon 53. AZL Opposition 1, Paper 392, 21:12-16.

Exhibit 3 to NS's Response to Sarepta's MIL No. 1

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: January 5, 2018
Electronic Signature for Amy E. Mandragouras, Esq.: /Amy E. Mandragouras, Esq./

Docket No.: AVN-008CN41 (PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Stephen Donald Wilton *et al.*

Application No.: 15/705,172 | Confirmation No.: 2879

Filed: September 14, 2017 | Art Unit: 1674

For: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF | Examiner: K. Chong

MS Amendment
Commissioner for Patents
P.O. Box 1450
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AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

Dear Sir:

In response to the Office Action dated October 5, 2017 (Paper No. 20171001), please amend the above-identified U.S. patent application as follows:

The **Listing of the Claims** begins on page 2 of this paper.

Remarks/Arguments begin on page 3 of this paper.

LISTING OF THE CLAIMS

1. **(Canceled)**

2. **(Previously Presented)** An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.

3. **(Previously Presented)** A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

REMARKS

Claims 2 and 3 are pending in the application. Applicants respectfully request reconsideration and withdrawal of the rejections as discussed below. Should the Examiner agree, she is urged to call the undersigned to address any outstanding double patenting rejections to expedite prosecution of this application.

Claim Rejections - 35 USC § 103

Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being obvious over van Ommen *et al.* (WO 2004/083432) and Koenig *et al.* (Nature 338, 509 - 511 06 April 1989). Applicants respectfully traverse this rejection based on the following remarks.

The Office failed to establish a prima facie case of obviousness

The Office bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. (MPEP §2142, 9th Ed.) "The Federal Circuit has stated that 'rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" (*Id.* citing *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006); see also *KSR*, 550 U.S. at 418, 82 USPQ2d at 1396 (quoting Federal Circuit statement with approval).)

"Obviousness is a question of law with underlying factual findings, including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the pertinent art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence such as commercial success, long-felt need, and the failure of others." (*KSR Int'l Co. V. Teleflex, Inc.*, 550 U.S. 398 (2007) citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).) With respect to the third inquiry, to establish a *prima facie* case of obviousness, the Office must identify both a reason why a person of ordinary skill in the art would have combined the prior art elements to arrive at the claimed subject matter, and a reason why one of ordinary skill in the art would have considered the outcome predictable. (*KSR Int'l Co. V. Teleflex, Inc.*, 550 U.S. 398 (2007).)

"In cases involving the patentability of a new chemical compound, *prima facie* obviousness under the third *Graham* factor generally turns on the structural similarities and differences between the claimed compound and the prior art compounds." According to

established Federal Circuit precedent, a two-part "lead compound" analysis must be satisfied to establish a *prima facie* case of obviousness. (*Otsuka Pharmaceutical Co. Ltd., v. Sandoz, Inc.*, 678 F.3d 1280 (2012).) To satisfy the lead compound analysis, the Office must establish: (1) that one of ordinary skill in the art would have selected the asserted prior art compound as a lead compound for further development, and (2) that the prior art would have motivated one of ordinary skill in the art to modify the lead compound to make the claimed compound with a reasonable expectation of success. (*Id.* at 1291-1292.)

For the reasons below, neither prong of the two part inquiry has been met in the present case. The first prong is not met because the Office failed to provide a reason why one of ordinary skill in the art would have selected SEQ ID NO: 29 ("h53AON1") of van Ommen et al. as a lead compound. The second prong is not met because, even assuming that one of skill in the art would have selected h53AON1 as a lead compound, the Office failed to provide a reason or motivation to specifically ***lengthen*** h53AON1 by **nine** additional bases of SEQ ID NO: 195 to arrive at the limitation of claim 1 that the base sequence comprises at least 12 consecutive bases of SEQ ID NO: 195.[1] Moreover, there was a significant level of unpredictability associated with selecting a specific antisense oligonucleotide to induce effective exon skipping of human dystrophin pre-mRNA at the time of the invention, and therefore no reasonable expectation of success.

Lead Compound Analysis

i. The Office failed to provide a reason why a person of ordinary skill in the art would have selected h53AON1 as a lead compound

A lead compound is "a compound in the prior art that would be most promising to modify in order to improve upon its…activity and obtain a compound with better activity.'" (*Otsuka Pharmaceutical Co. Ltd., v. Sandoz, Inc.*, at 1291 (citing *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)).) "[A] reason to select a compound as a lead compound depends on ***more than just structural similarity***…" *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc.*, 923 F.Supp.2d 602 at 657 (2013) (citing Matrix Labs., 619 F.3d at 1354; emphasis added). Notably, it has been held that "absent

[1] Applicants note and further explain below that, contrary to the position of the Office, the skilled artisan must lengthen h53AON1 by nine nucleotides, not two nucleotides, of SEQ ID NO: 195 to achieve the requirement of at least 12 bases of SEQ ID NO: 195 recited by the instant claims.

a reason or motivation based on such prior art evidence, ***mere structural similarity*** between a prior art compound and the claimed compound ***does not inform the lead compound selection***." (*Otsuka Pharmaceutical Co. Ltd., v. Sandoz, Inc.*, at 1292 (citing *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010)); emphasis added.)

The Office has not provided any evidence or reasoning to support the conclusion that a person of ordinary skill in the art would have selected h53AON1 as the lead compound. Instead, the Office simply chooses it as its basis for the alleged obviousness of the claimed subject matter. Thus, its' selection by the Office in the absence of any supporting evidence or reasoning as a lead compound can only be through impermissible hindsight. Accordingly, the Office has not established that a person of ordinary skill in the art would select h53AON1 as the lead compound to modify to arrive at the claimed antisense oligonucleotides. For this reason alone, the claims are not *prima facie* obvious over the cited documents, and the Office should therefore withdraw the rejection.

ii. The cited art does not motivate a person of ordinary skill in the art to modify h53AON1 to make the claimed antisense oligonucleotides with a reasonable expectation of success

Even if the Office had established that a person of ordinary skill in the art would have selected h53AON1 as the lead compound, the second prong of the test also has not been met. The second prong of the lead compound analysis requires a determination of whether "the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound with a reasonable expectation of success." (*Otsuka Pharmaceutical Co. Ltd., v. Sandoz, Inc.*, 678 F.3d at 1292 (2012).)

The Office relies on van Ommen et al. as teaching a genus of oligonucleotides 16-50 bases in length that are complementary to, and cause skipping of, exon 53, and selects SEQ ID NO: 29 (h53AON1), which it contends is a 18-mer oligonucleotide having a sequence identical to three nucleotides of SEQ ID NO: 195. The Office contends, "[i]t would have been obvious for one of ordinary skill in the art to make an antisense oligonucleotide of 20-31 bases" using "the sequence of h53AON1 to arrive at an oligonucleotide of **20** nucleotides and having **12** nucleotides of SEQ ID No. 195. . ." by "preparing obvious variants of h53AON1 to try to **optimize** the activity of the oligonucleotide. . ." using "common and efficient strategies" such as

synthesizing and testing "longer oligonucleotides containing within them" h53AON1. (*See* Office Action at pages 4-5 (emphasis added).)

Applicants submit that a person of ordinary skill in the art would not have been motivated to modify h53AON1 of van Ommen et al. to arrive at the claimed morpholino antisense oligonucleotides, and certainly not with a reasonable expectation of success. Notably, none of the cited documents would have motivated one of ordinary skill in the art to ***increase the length*** of the 18-mer h53AON1 to 27 bases 100% complementary to the exon 53 target region +23 to +69 and, let alone select at least 12 consecutive bases of SEQ ID NO: 195 and ***thymine bases*** in place of uracil bases, and select a ***morpholino*** chemistry backbone rather than a 2'-O-methyl phosphorothioate ("2'-O-Me-PS").[2]

Importantly, Applicants respectfully point out that the Office's proposed strategy for modification of h53AON1 by lengthening it by only two bases would not result in an antisense oligonucleotide within the scope of the instant claims. To illustrate this point, Applicants provide the following alignment of h53AON1 (line 2) to SEQ ID NO: 195 (line 1).

1. CUGAAGGUGUUCUUGUACUUCAUCC SEQ ID NO: 195
2. CUGUUGCCUCCGGUUCUG h53AON1
3. CUGUUGCCUCCGGUUCUGAA h53AON1+**2** bases = 20mer
4. CUGUUGCCUCCGGUUCUGAAGGUGUUC h53AON1+**9** bases = 27mer

As can be seen from above and acknowledged by the Office, h53AON1 comprises only three consecutive bases of SEQ ID NO: 195 indicated in the underlined portion of lines 1 and 2. Addition of **two** additional consecutive bases to h53AON1 as proposed by the Office results in a 20mer that is within the claimed length range, but such a 20mer would only comprise **five** consecutive bases of SEQ ID NO: 195 as illustrated in line 3 – not at least 12 consecutive bases of SEQ ID NO: 195 as required by the claims. Applicants note that to achieve an antisense oligonucleotide of the instant claims comprising, *inter alia*, at least 12 bases of SEQ ID NO: 195, the skilled artisan would need to, *inter alia*, lengthen h53AON1 by 9 bases as illustrated in the underlined portion of line 4 above. Meaning, simply lengthening h53AON1 by two bases as suggested by the Office would clearly **not** result in the claim requirement of at least 12 bases of

[2] Nor can it be found that the claimed invention would have been "obvious to try" as there are ***not*** a "***finite number of identified, predictable solutions"*** such that one ordinarily skilled in the art could have pursued known potential solutions with a reasonable expectation of success. (*Examination Guidelines Update: Developments in the Obviousness Inquiry after KSR v. Teleflex*, issued by the United States Patent and Trademark Office (Federal Register, Vol. 75, No. 169: 53643, September 1, 2010); emphasis added.)

SEQ ID NO: 195. Applicants base the remainder of the response based on modifying h53AON1 by, *inter alia*, adding 9 consecutive bases of SEQ ID NO: 195.

With regard to van Ommen et al., it cannot be said that there were a "finite number" of known, predictable solutions to the problem of designing a more efficient exon skipping antisense oligonucleotide with a reasonable expectation of success. In fact, van Ommen et al. suggest a wide variety of modifications to the antisense oligonucleotide structure with little specificity as to any individual oligonucleotide in the following:

> [t]he complementary oligonucleotide generated through a method of the invention is preferably complementary to a consecutive part of between ***16 and 50 nucleotides*** of the exon RNA. ***Different types of nucleic acid may be used*** to generate the oligonucleotide. Preferably, the oligonucleotide comprises RNA, as RNA/RNA hybrids are very stable. Since one of the aims of the exon skipping technique is to direct splicing in subjects, it is preferred that the oligonucleotide RNA comprises a ***modification providing the RNA with an additional property***, for instance, resistance to endonucleases and RNaseH, additional hybridization strength, increased stability (for instance, in a bodily fluid), increased or decreased flexibility, reduced toxicity, increased intracellular transport, and/or tissue-specificity, etc. Preferably, the modification comprises a 2'-O-methyl-phosphorothioate oligoribonucleotide modification.
> With the advent of ***nucleic acid-mimicking technology***, it has become possible to generate molecules that have a similar, preferably the same, hybridization characteristics, in kind, not necessarily in amount, as nucleic acid itself. Such equivalents are, of course, also part of the invention. ***Examples of such mimics*** equivalents are ***peptide nucleic acid, locked nucleic acid and/or a morpholino phosphorodiamidate***. . . . ***Hybrids between one or more of the equivalents among each other and/or together*** with nucleic acid are, of course, also part of the invention. In a preferred embodiment, an equivalent comprises locked nucleic acid, as locked nucleic acid displays a higher target affinity and reduced toxicity and, therefore, shows a higher efficiency of exon skipping. (van Ommen et al. page 9, line 28 to page 11, line 2; emphasis added.)

van Ommen et al. also teach that "[i]t is thus not absolutely required that all the bases in the region of complementarity are capable of pairing with bases in the opposing strand....***[m]ismatches may to some extent be allowed***." (van Ommen et al. at page 3, ll. 3-8; emphasis added.) van Ommen et al. does not require that additional bases added to the antisense oligonucleotide be complementary to exon 53. *Id.*

Thus, there are a tremendous number of possible solutions to modify h53AON1 based on the length and position of "16-50 bases," mismatches, and many possible variations at any of three "substituents" (*i.e.*, nucleobase, ribose ring and phosphate linkage). Even if one focuses on

the nucleobase sequence, assumes the chemical backbone and internucleotide linkages are unmodified, and limits the number of possible bases to those found in RNA, as shown in h53AON1, adding a single nucleobase to a 18-mer yields 8 possible sequence combinations (A, C, G, or U added before or after the 18-mer.)[3] Adding two nucleobases yields 64 possible combinations. Adding three nucleobases yields 256 combinations. Adding 9 nucleobases to obtain a 27-mer yields 2,621,440 possible combinations. And, adding 32 nucleobases to obtain a 50-mer yields 608,742,554,432,415,200,000 possible combinations.

Of course, this significantly *underestimates* the number of possible nucleobase combinations because van Ommen et al. specify "different types of nucleic acid," and is not limited to the "natural" bases A, C, G, and U found in RNA, but includes other naturally-occurring and non-naturally occurring nucleobases such as inosine, hypoxanthine, xanthine, and many others. Different types of nucleic acid also include nucleotide analogs and chemical modifications to the backbone, as all of the working examples by van Ommen et al. use 2'-O-Me-PS oligoribonucleotide modifications. Different types of nucleic acid also include "mimetics" such as peptide nucleic acids, locked nucleic acid, and morpholino phosphorodiamidates. (van Ommen et al. at page 10, ll. 11-16.) Given the incredibly large number of modifications to h53AON1 that are taught by the cited documents the only way to start from h53AON1 and modify it to arrive at the claimed antisense oligonucleotide is by the application of hindsight.

There is also no reason or motivation to specifically ***increase*** the length of h53AON1 as there is no teaching in van Ommen et al. with respect to the effects on exon skipping of ***lengthening*** (or shortening) an antisense oligonucleotide. In fact, as shown in Table 2, all of the antisense oligonucleotides with exon skipping activity are ***15-24 bases in length***, and all but 3 of those are between ***17 and 20 bases***, almost two thirds are either ***19 or 20 bases***, and ***none are 25 bases in length***. (van Ommen et al. Table 2 at page 48.) As the vast majority of the antisense oligonucleotides tested by van Ommen et al. in Table 2 are ***20 bases or less*** (25/30), one of ordinary skill in the art would have no reason or motivation to lengthen h53AON1 at all. In fact, one skilled in the art would be equally motivated to shorten h53AON1, as almost two thirds of

[3] Assuming only the four RNA nucleobases, the number of nucleobase combinations for a particular length AON can be calculated by this formula, where "n" equals the number of bases being added to the chain: $(4^n) \times (n+1)$. This is because each additional nucleotide can be added to either end of SEQ ID NO: 29.

the antisense oligonucleotides are either 19 or 20 bases, and the shortest antisense oligonucleotide with activity in Table 2 is 15 bases (h46AON4b).

Moreover, the Office failed to provide a reason why the skilled artisan would lengthen h53AON1. Instead, the Office merely concludes the skilled artisan would "prepare obvious variants of h53AON1 to try to optimize the activity of the oligonucleotide" and that the skilled artisan would "try" to enhance activity by "a common and efficient strategy" of synthesizing and testing "longer oligonucleotides containing within them the sequence known to have the desired activity." Office Action at pages 4-5. The Office overlooks the fact that in Table 2 the only other antisense oligonucleotide made and tested by van Ommen et al. is h53AON2, and this antisense oligonucleotide – like h53AON1 – is an 18mer. Applicants respectfully point out that "[a] particular parameter must first be ***recognized*** as a ***result-effective variable***, i.e., a variable which achieves a ***recognized*** result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." M.P.E.P. 2144.05(II)(B) (emphasis added); *see* also *In re Antonie*, 559 F.2d 618, 195 U.S.P.Q. 6 (CCPA 1977).

In the present case, the Office failed to satisfy its burden of providing evidence that oligonucleotide length was recognized in the prior art as a result effective variable for exon 53 skipping and activity in treatment for DMD. See *id.* Absent such evidence of recognition as a "result-effective variable[,]" it is not, therefore, routine optimization "within the skill of the artisan" to vary the length of an oligonucleotide to optimize exon 53 skipping and activity in the treatment of DMD. See M.P.E.P. 2144.05(II)(B); *In re Antonie*, 559 F.2d 618, 620, 195 U.S.P.Q. 6, 8-9 (C.C.P.A. 1977) (optimization of a parameter not recognized as a result-effective variable is an exception to the rule that "discovery of an optimum value of a variable in a known process is normally obvious"). Thus, the Office's proffered rationale of routine optimization by lengthening h53AON1 does not apply.

Given the length of 16-50 bases and the many possible variations in nucleobase and backbone chemistry taught by van Ommen et al., there is ***not*** a "finite number" of known, predictable solutions to modifying h53AON1 such that one of ordinary skill in the art would arrive at the claimed morpholino antisense oligonucleotides of 20 to 31 bases having a base sequence 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), and having at least 12 consecutive bases of SEQ ID NO: 195 in which uracil bases are thymine bases, with a reasonable expectation of success. In fact, there is

absolutely nothing in van Ommen et al. about selecting a morpholino chemistry backbone and thymine bases, rather than uracil bases.

iii. High level of unpredictability in the field with no reasonable expectation of success

Even assuming, *arguendo*, that one of ordinary skill would have selected h53AON1 of van Ommen et al. as a lead compound and would have been motivated to modify it in the particular way necessary to arrive at the subject matter of the claims, there would be no reasonable expectation of success because at the time the instant invention was made, there was a significant level of unpredictability associated with selecting specific antisense oligonucleotide sequences to induce effective dystrophin exon skipping. For example, the specification as originally filed notes that the size or length of an antisense oligonucleotide is not predictive of its efficacy (specification at page 21, lines 11-12). In addition, Applicants have found that there is no standard motif that can be blocked or masked by antisense molecules to redirect splicing (specification at page 21, lines 18-20). Applicants submit that the cited art does not provide sufficient guidance to arrive at the claimed subject matter considering the high level of unpredictability in the art.

Applicants refer the Office to van Deutekom *et al.* (2003) Nature Reviews, 4:774-783 ("van Deutekom Review"; submitted in an Information Disclosure Statement on September 22, 2017). This article is a review that generally discloses exon skipping in the dystrophin gene. The van Deutekom Review notes that interfering with exon selection for inclusion before splicing is "a process that is ***not yet well understood***" (page 780, col. 1, lines 1-3, emphasis added).

Applicants also refer the Office to U.S. Patent Application Publication No. 2006/0147952 to van Ommen et al. (the '952 Publication) describe an approach in which "AONs were ***empirically analyzed*** for the induction of exon skipping." ('952 Publication at [0051]; emphasis added.) Such an approach relies on experience or observation and provides no indication as to what parameters are critical for the design of exon skipping antisense. As each antisense oligonucleotide must be empirically analyzed, the results are ***unpredictable*** as reported in Table 2 of the '952 Publication:

> [t]heir different lengths and G/C contents (%) ***did not correlate to their effectivity in exon skipping*** (1, induced skipping, 2, no skipping). The AONs were directed to purine

> (A/G)-rich sequences as indicated by their (antisense) U/C content (%). Skipping of the target exons resulted in either an in-frame (IF) or out-of-frame (OF) transcript. (van Ommen et al. [0153], Table 2, footnote *a*; emphasis added.)

Additional evidence of unpredictability is found by analyzing the antisense sequences in Table 2 of the '952 Publication. For example, the two antisense oligonucleotides designed to induce skipping of exon 2 have overlapping nucleotide sequences:

```
h2AON1                          cccauuuugugaauguuuucuuuu
h2AON2          uugugcauuuacccauuuugug
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Despite the overlap in sequence, h2AON1 purportedly induced skipping, while h2AON2 did ***not***. ('952 Publication at Table 2.) And yet for another pair of overlapping AONs, both members of the pair did purportedly induce skipping:

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h29AON1                 uauccucugaaugucgcauc
h29AON2           gguuauccucugaaugucgc
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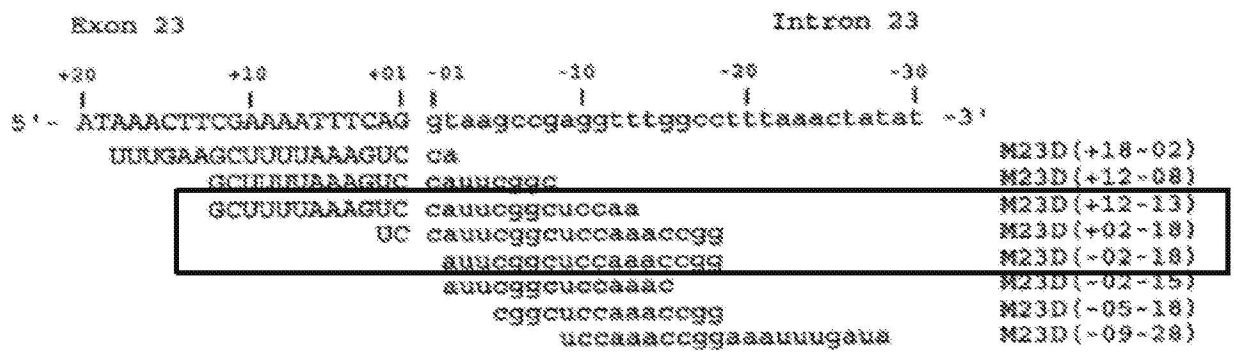
There is no explanation in the '952 Publication for these disparate results.

Much of the data in Table 2 of the '952 Publication was published in 2002 by Aartsma-Rus et al. (Neuromuscular Disorders, 12:S71-S77 (2002) ("Aartsma-Rus (2002)"; submitted in an Information Disclosure Statement on September 22, 2017). Aartsma-Rus (2002) discloses two specific oligonucleotides directed at dystrophin exon 53 and notes that there is ***no correlation*** between the length or sequence of the oligonucleotide and its effectiveness at inducing exon skipping. (Aartsma-Rus (2002) at page S76, col. 1, lines 43-45.) Still further, Aartsma-Rus (2002) teaches that ***significant experimentation is required*** to arrive at specific oligonucleotides, noting that "[w]e therefore have ***no insight*** into the actual position of the targeted sequence within the completely folded RNA structure. Its accessibility, and thus the effectivity of any designed AON, will therefore have to be tested ***empirically*** in the cells, as was done in this study." (Aartsma-Rus (2002) at page S76, col. 1, lines 4-6; emphasis added.)

Another study, co-authored by one of the Applicants, examined skipping of exon 23 from the mouse DMD gene by RT-PCR following transfection with a series of overlapping 2'-Me-O-PS AONs, as shown in the following figure. Of the antisense oligonucleotides tested, only M23D(+12-13), M23D(+02-18), and M23D(-02-18) were effective in inducing detectable exon

skipping. (Mann et al., J. Gene Med., 4(6): 644-654 (2002); submitted in an Information Disclosure Statement on September 22, 2017.)



(Mann et al. at 646.) Notably, the ***shorter*** antisense oligonucleotide M23D(-02-18), which is only ***17 nucleotides*** in length, was particularly efficient at inducing skipping and was reported to induce exon skipping at concentrations as low as 5 nM. The authors concluded that they could improve "the efficiency of the technique" by "***reduc[ing] the size*** and the effective dose of the AO[N]s" examined. (Mann et al. at 644; emphasis added.)

Similar examples of unpredictability were reported by van Ommen et al. and other investigators at or near the date of Applicants' invention. In a 2005 publication the same design rationale described by van Ommen and coworkers was applied again. (Aartsma-Rus et al. Oligonucleotides, 15(4): 284-297 (2005) ("Aartsma-Rus (2005)"; submitted in an Information Disclosure Statement on September 22, 2017.) Table 1 of Aartsma-Rus (2005) provides the sequences of the antisense oligonucleotides and whether or not they induced skipping. (Aartsma-Rus (2005) at 285, first and second columns.) The following pairs of antisense oligonucleotides are found in the Table (+ and – refer to skipping ability):

h29AON10	guaguucccuccaacg	–
h29AON11	cauguaguucccucc	+
h43AON2	uuguuaacuuuuucccauu[4]	+

[4] There is a discrepancy between the disclosure of Aartsma-Rus (2005) and the sequence as shown by van Ommen et al. In the 2005 publication, the sequence is shown as uuguuaacuuuuuccauu, while in Table 2

h43AON3	uguuaacuuuuucccauugg	-
h46AON8	gcuuuucuuuuaguugcugc	++
h46AON9	uuaguugcugcucuu	-
h48AON3	ggucuuuuauuugagcuuc	-
h48AON7	uuuauuugagcuucaaauuu	+

It is evident from these results that applying the design rationale described by van Ommen et al. is a hit-or-miss proposition in terms of whether any given antisense oligonucleotide will be capable of inducing skipping, ***even in situations where the antisense oligonucleotides are very similar to each other in terms of nucleotide sequence, and other variables concerning the chemical backbone are fixed***. All of the antisense oligonucleotides described in the study "contain 2'-O-methyl RNA and full-length phosphorothioate (PS) backbones." (Aartsma-Rus (2005) at 285.) None of the antisense oligonucleotides disclosed were longer than 24 nucleotides, and the majority of the antisense oligonucleotides were 20 nucleotides in length or shorter. (Aartsma-Rus at Table 1.) None of these antisense oligonucleotides include non-natural bases. Given the common chemical modifications of these antisense oligonucleotides, the data reported in this paper demonstrates the unpredictable impact that length and nucleotide composition make with respect to efficiency in inducing exon skipping.

The recognition of the lack of predictability in the field of exon skipping continued beyond 2005. A 2007 paper co-authored by van Ommen co-inventors Aartsma-Rus and van Deutekom states that "several years after the first attempts at dystrophin exon skipping with AOs [antisense oligonucleotides], ***there are still no clear rules to guide investigators in their design***, and in mouse and human muscle cells *in vitro* ***there is great variability for different targets and exons***." (Arechavala-Gomeza et al. Hum. Gene Ther., 18(9): 798-810, 807 (2007); submitted in an Information Disclosure Statement on September 22, 2017; emphasis added.)

And again in 2009 van Ommen and co-workers wrote that while existing software programs can facilitate design, "in general ***a trial and error procedure*** is still involved to

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of van Ommen et al. it shown as above having a sequence of "ccc" toward the 3' end of the AON. It is assumed the latter is correct as it corresponds to the sequence of h43AON3.

identify potent AONs." (Aartsma-Rus et al., Mol. Ther., 17(3):548-553 (2009) at 548; submitted in an Information Disclosure Statement on September 22, 2017; emphasis added.)

Evidence that selecting specific antisense oligonucleotide sequences to induce effective dystrophin exon skipping remains an unpredictable exercise is also found in a 2011 publication by Wu *et al.* (2011) *PLoS One*, 6(5): e19906 (submitted in an Information Disclosure Statement on September 22, 2017). Although Wu *et al.* is evidence developed after the instant filing date, the level of unpredictability in the art directly relates to whether the results obtained with any specific species would be unexpected and courts have held that it is not "improper to conduct additional experiments and provide later-obtained data in support of patent validity." *Knoll Pharm. Co., Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004). Evidence of the lack of predictability of in the field is relevant to the non-obviousness of the claimed antisense oligonucleotides over the cited art.

Wu *et al.* describe a systematic approach for identifying antisense oligonucleotides of high efficacy in inducing dystrophin exon skipping. Wu *et al.* designed 25 antisense oligonucleotides (AOs) to cover more than two thirds of exon 50 of the human dystrophin gene and the two flanking intron sequences. Wu *et al.* determined the efficiency of AO-induced skipping of exon 50 by comparing the activity of a series of AOs. Table 1 on page 4 of the publication summarizes all the AOs tested, including both 2'-O-methyl phosphorothioate and morpholino antisense oligonucleotides, as well as their reported activity in two assays. The exon skipping effect was determined using both a GFP reporter cell line with GFP expression coupled to exon 50 skipping and normal human myoblasts.

As shown in Table 1, Wu *et al.* tested AOs having a common 5' or 3' termini, but varied in length. Shown below is an excerpt from Table 1 of Wu *et al.*

hE50 AO2PS	−19−1	5'-CUUUAACAGAAAAGCAUAC-3'	19 bp	-	-	N/D
hE50 AO3PS	−19+1	5'-UCUUUAACAGAAAAGCAUAC-3'	20 bp	-	-	N/D
hE50 AO4PS	−19+3	5'-CCUCUUUAACAGAAAAGCAUAC-3'	22 bp	4%	3%	N/D
hE50 AO5PS	−19+8	5'-AACUUCCUCUUUAACAGAAAAGCAUAC-3'	27 bp	21%	29%	N/D
hE50 AO6PS	−19+13	5'-CUUCUAACUUCCUCUUUAACAGAAAAGCAUAC-3'	32 bp	3%	<1%	N/D

Each of these AOs target exon 50 starting at position (-19) and ending at position (-1), (+1), (+3), (+8) and (+13), respectively, and the oligonucleotides overlap at the 3' end. These AOs varied in length from 19 to 32 bases and the data shows that increasing AO length does not

necessarily increase exon skipping activity and there is no reasonable expectation of success in increasing AO length to obtain increased exon skipping activity. For example, the 19- and 20-mer AOs hE50 AO2PS and hE50AO3PS were inactive. Increasing the length to 22 and 27 bases (hE50 AO4PS and hE50 AO5PS, respectively) resulted in increased activity, but a further increase to 32 bases (hE50 AO6PS) decreased activity significantly. Specifically, hE50 AO5PS is 5 nucleotides longer than hE50 AO4PS, but the level of GFP of hE50 AO5PS is 17% higher with respect to GFP assay and 26% higher with respect to human myoblasts. hE50 AO5PS is 5 nucleotides shorter than hE50 AO6PS, but the level of GFP of hE50 AO5PS is 18% higher with respect to GFP and 28% higher with respect to human myoblasts.

The data provided in Table 1 also demonstrate that when hE50 AO4PS (-19+3) was extended five nucleotides in length to hE50A AO5PS (-19+8), activity was increased. Notably, however, the addition of yet another five nucleotides to hE50 AO6PS (-19+13) essentially eliminated the activity.

In yet another example, a relatively short oligonucleotide (hE50 AO19PS; +97-5) at the 3' end of the exon showed low activity (3%) with respect to GFP, and activity did not increase when the oligonucleotide was lengthened by five or nine nucleotides at the 5' end (hE50 AO20PS and hE50 AO21PS, respectively) or by five nucleotides in the 3' direction (hE50 AO16PS). These four antisense oligonucleotides showed no activity in the human myoblasts. Thus, Wu *et al.* demonstrate that increasing or decreasing AO length results in unpredictable effects on exon skipping.

Importantly, the Patent Trial and Appeal Board (PTAB) in Interference No. 106,007 ("the '007 interference") concerning exon 53 antisense oligonucleotides for DMD held that the field of antisense oligonucleotides for exon skipping for DMD was unpredictable at the time the instant application was filed. Its decision was based on the foregoing evidence and expert testimony. *See* Decision on Motions in Interference No. 106,007 (exon 53) dated May 12, 2016 (decision final upon withdrawal of CAFC Appeal No. 2016-2262; Decision on Motions previously submitted in an Information Disclosure Statement on September 22, 2017). Specifically, the PTAB determined that sequence length of antisense oligonucleotides that would maintain exon skipping was substantially unpredictable at the time US Application No. 11/233,495 was filed by Academisch Ziekenhis Leiden ("AZL"). See *id.* at page 5, line 26 to page 6, line 3. Applicants note that the '495 application claims priority to the van Ommen *et al.* PCT application presently cited by the Office. In its Decision, the PTAB

considered the foregoing evidence as representative of the state of the art with Exhibits 2010 and 2015 in Interference 106,007 corresponding to Aartsma-Rus and Wu *et al.*, submitted herewith as Appendices A and C, respectively. Unpredictability in this art was determined by the PTAB to have existed at the time of the instant invention (and years afterwards).

Upon consideration of this evidence, the PTAB stated "[t]he evidence indicates that at the time AZL filed its application, the identification of AONs that will cause exon skipping was generally thought to be **unpredictable**. One of the significant factors causing that unpredictability is the effect of the number of nucleobases present in the AON." (Decision on Motions at page 17 (emphasis added)). In particular, the relationship between length of a base sequence and the ability of an antisense oligonucleotide to induce exon skipping was considered by the PTAB.

Despite the unpredictability in the art, the PTAB found obvious a 20mer AON based on SEQ ID NO: 193 over a completely overlapping 18mer (h53AON1). In this particular circumstance, the PTAB found that "a degree of exon skipping capability would likely be maintained due to a change in a ***small number of complementary nucleobases*** of an AON known to cause skipping" and, therefore, concluded "[i]t would have been obvious, for example, to add the ***two*** complementary nucleobases dictated by the known sequence of exon 53 to either end of h53AON1 with a reasonable expectation that the resultant 20 base AON would cause exon skipping." *Id.* at pages 41-42 (emphasis added).

In contrast to the narrow issue considered by the PTAB described above, the PTAB does not support a determination of obviousness of the instant claims. The PTAB's determination of unpredictability still applies. And to arrive at the instantly claimed antisense oligonucleotides, a person of ordinary skill would have to modify h53AON1 by adding at least ***9 bases*** (and would have to do so with a reasonably expectation of success). Such a modification in length cannot be said to be predictable under the Decision in the '007 interference. Accordingly, it would not have been obvious to extend h53AON1 by 9 bases at least because of the highly degree of unpredictability discussed above, and the Office failed to provide evidence to the contrary.

Furthermore, similar to the Office's assertion, AZL argued that upon identification of h53AON1, "one skilled in the art would have investigated extended complementary sequences with the expectation that the longer sequences would bind and cause skipping." *Id.* The PTAB did not find this argument persuasive at least because AZL failed to provide any

evidence to support the basis for this expectation. *Id.* at page 18. Like AZL, the Office failed to provide evidence to support this argument. *See* Office Action at page 5. Accordingly, Applicants urge the Office to adopt the PTAB's determination of unpredictability in the field of exon skipping for DMD.

In summary, the van Deutekom Review, Aartsma-Rus and Wu *et al.* references, along with the Decision on Motions in the '007 interference, serve to illustrate the unpredictability associated with selecting ***specific*** antisense oligonucleotides that are effective for inducing skipping of dystrophin exons. Accordingly, the Office failed to establish a *prima facie* case of obviousness with respect to the predictability of the outcome in combining teachings of van Ommen *et al.* and Koenig *et al.* in the manner proposed to arrive at the claimed invention.

In view of the preceding remarks, Applicants submit that the Office failed to establish a *prima facie* case of obviousness based on the cited art. As such, Applicants respectfully request reconsideration and withdrawal of this obviousness rejection.

Double Patenting

Claims 2 and 3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 8,455,636. Applicants respectfully traverse this rejection.

The Office asserts "the instant claims and the claims of the patent are drawn to antisense oligonucleotides having at least 17 consecutive bases of SEQ ID No. 193." Office Action at page 6. However, Applicants note the instant claims are drawn to antisense oligonucleotide having 20-31 bases and comprising at least 12 consecutive bases of SEQ ID NO: ***195***. Moreover, the '636 patent is directed to an antisense oligonucleotide comprising 20-50 bases and at least 20 consecutive bases of SEQ ID NO: ***193***. As such, Applicants point out that there is only a **9** base overlap between SEQ ID NOs: 193 of the '636 Patent and SEQ ID NO: 195 of the instant claims. Accordingly, Applicants respectfully request that the Office consider withdrawing the instant rejection in view of these facts and the foregoing remarks.

Claims 2 and 3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 8,232,384. Applicants respectfully request clarification of this rejection. Specifically, The Office asserts

"the instant claims and the claims of the patent are drawn to antisense oligonucleotides having at least 17 consecutive bases of SEQ ID No. 193." Office Action at page 7. However, Applicants note the instant claims are drawn to antisense oligonucleotide having 21-30 bases and comprising at least ***12*** consecutive bases of SEQ ID NO: ***195***. Moreover, the '384 patent is directed to an antisense oligonucleotide *consisting* of SEQ ID NO: 195. Accordingly, Applicants respectfully request clarification.

CONCLUSION

In view of the foregoing, Applicants respectfully submit that the pending claims are in condition for allowance. If a telephone conversation with Applicants' attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 217-4626. If a fee is due with this submission, please charge our Deposit Account No. 12-0080 under Order No. AVN-008CN41, from which the undersigned is authorized to draw

Dated: January 5, 2018

Respectfully submitted,
Electronic signature: /Amy E. Mandragouras, Esq./
Amy E. Mandragouras, Esq.
Registration No.: 36,207
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4626
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

Office Action Summary

Application No.	Applicant(s)		
15/705,172	WILTON et al.		
Examiner	**Art Unit**	**AIA Status**	
KIMBERLY CHONG	1674	No	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 01/05/2018.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 2-3 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 2-3 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 01/05/2018.

3) ☑ Interview Summary (PTO-413) Paper No(s)/Mail Date 03/26/2018.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Status of Application/Amendment/Claims

Claims 2 and 3 are pending and currently under examination.

Information Disclosure Statement

The submission of the Information Disclosure Statements on 01/05/2018 is in compliance with 37 CFR 1.97. The information disclosure statement has been considered by the examiner and signed copies have been placed in the file.

Response to Arguments

Claim Rejections - 35 USC § 103

The rejection of claims 2 and 3 under pre-AIA 35 U.S.C. 103(a) as being obvious over van Ommen (WO2004/083432 cited on IDS filed 09/22/2017) and Koenig et al. (Nature 338, 509 - 511 06 April 1989 cited on IDS filed 09/22/2017) is withdrawn in response to Applicant's argument that one of skill in the art would not have been motivated to make the claimed oligonucleotide from h53AON1 taught by van Ommen.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11

F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

The rejection of claims 2 and 3 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 8,455,636 is withdrawn in response to Applicant's arguments.

The rejection of claims 2 and 3 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 8,232,384 is maintained for the reasons of record.

Patent '384 are drawn to an antisense oligonucleotide targeted to annealing site H53A (+23+47) and consisting of SEQ ID No. 195 which is 25 nucleotides in length. The instant claims are drawn to an antisense oligonucleotide targeted to annealing site H53A (+23+47) having20-31 bases comprising at least 12 consecutive bases of SEQ ID No. 195 but could also encompass 25 nucleotides of SEQ ID No. 195. Therefore the instant claims and the claims of the patent are not patentably distinct from each other.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KIMBERLY CHONG **whose telephone number is** (571)272-3111**.** The examiner can normally be reached Monday thru Friday 9-5 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact the SPE for 1674 Ram Shukla at 571-272-07350735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/
Primary Examiner
Art Unit 1674

Exhibit 4 to NS's Response to Sarepta's MIL No. 1

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/705,172	09/14/2017	Stephen Donald WILTON	AVN-008CN41	2879

123147 7590 10/05/2017

Nelson Mullins Riley & Scarborough LLP/Sarepta
One Post Office Square
Boston, MA 02109

EXAMINER
CHONG, KIMBERLY

ART UNIT	PAPER NUMBER
1674	

NOTIFICATION DATE	DELIVERY MODE
10/05/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Office Action Summary

Application No.	Applicant(s)		
15/705,172	WILTON ET AL.		
Examiner	**Art Unit**	**AIA (First Inventor to File) Status**	
KIMBERLY CHONG	1674	No	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09/26/2017*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *2 and 3* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *2 and 3* are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *09/14/2017* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *09/22/2017*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Status of Application/Amendment/Claims

Claims 2 and 3 are pending and currently under examination.

Information Disclosure Statement

The submission of the Information Disclosure Statements on 09/22/2017 is in compliance with 37 CFR 1.97. The information disclosure statement has been considered by the examiner and signed copies have been placed in the file.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2 and 3 are rejected under pre-AIA 35 U.S.C. 103(a) as being obvious over van Ommen (WO2004/083432 cited on IDS filed 09/22/2017) and Koenig et al. (Nature 338, 509 - 511 06 April 1989 cited on IDS filed 09/22/2017).

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The claims are drawn to an antisense oligonucleotide of 20-31 bases comprising a base sequence 100% complementary to consecutive bases of exon 53 of the human dystrophin pre-mRNA, wherein the antisense oligonucleotide base sequence comprises at least 12 consecutive bases of SEQ ID NO: 195, wherein uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense induces exon 53 skipping. The claims are further drawn to a pharmaceutical composition comprising said antisense oligonucleotide.

van Ommen teach a genus of oligonucleotides 16-50 complementary to exon 53 and has identified an active range in the DMD gene and have shown two oligonucleotide h53AON1 and h53AON2 that cause skipping of exon 53 (see Table 2). van Ommen et al. teach the oligonucleotides can be complementary to the exon in the pre-mRNA. Thus given the sequence of the DMD gene has been identified, as demonstrated by Koenig et al., an oligonucleotide sequence complementary to that

portion of the mRNA is exactly determined by the simple base pairing rules of DNA and RNA (G being complementary to C, and A being complementary to T (or U)).

vanOmmen et al. the oligonucleotide can have modifications such as morpholino phosphorodiamidate, peptide nucleic acid and locked nucleic acids, for example, and further teach the oligonucleotide comprises modified internucleoside linkages (see claim 12 and page 23). The oligonucleotide taught by van Ommen et al. encompasses both DNA and RNA nucleic acids as well as nucleic acids that are a combination of DNA and RNA as stated on page 9: lines 9-10 “Any oligonucleotide fulfilling the requirements of the invention may be used to induce exon skipping in the DMD gene." van Ommen et al. teach different nucleic acids may be used to generate the oligonucleotide (see page 9 line 30 - page 10). Thus oligonucleotides in which uracil bases are thymine bases are encompassed in the meaning of ‘oligonucleotide’ taught by van Ommen et al.

It would have been obvious to one of ordinary skill in the art to make an antisense oligonucleotide of 20-31 bases comprising at least 12 bases of SEQ ID No. 195. Given van Ommen et al. teach a genus of oligonucleotides of up to 50 nucleotides in length, one of skill in the art would have been motivated to use the sequence of h53AON1 to arrive at oligonucleotides of 20 nucleotides and having 12 nucleotides of SEQ ID No. 195 (which overlaps with 3 nucleotides of h53AON1). Because van Ommen et al. has identified exon 53 and shown oligonucleotides targeting this region can cause exon skipping and because the mRNA sequence containing the exon 53 was known in the prior art, as shown by Keonig et al., the combination of these teachings

provides motivation to prepare obvious variants of h53AON1 to try and optimize the activity of the oligonucleotide to prepare the most effective therapeutic for treating DMD.

It would have been routine and a common strategy to try and enhance the oligonucleotide by identifying variants of that oligonucleotide that have a higher level of activity and a common and efficient strategy for doing so is to synthesize and test longer oligonucleotides containing within them the sequence known to have the desired activity.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP §

717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 2 and 3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 8,455,636. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of the patent are drawn to antisense oligonucleotides having at least 17 consecutive bases of SEQ ID No. 193.

Claims 2 and 3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of U.S. Patent No. 8,232,384. Although the conflicting claims are not identical, they are not patentably

distinct from each other because the instant claims and the claims of the patent are drawn to antisense oligonucleotides having at least 17 consecutive bases of SEQ ID No. 193.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

706.07(a) Final Rejection, When Proper on Second Action [R-07.2015]

Second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims, nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p). Where information is submitted in an information disclosure statement during the period set forth in 37 CFR 1.97(c) with a fee, the examiner may use the information submitted, e.g., a printed publication or evidence of public use, and make the next Office action final whether or not the claims have been amended, provided that no other new ground of rejection which was not necessitated by amendment to the claims is introduced by the examiner. See MPEP § 609.04(b).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Kimberly Chong whose telephone number is 571-272-3111.** The examiner can normally be reached Monday thru Friday 9-5 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact the SPE for 1674 Ram Shukla at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file

folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/
Primary Examiner
Art Unit 1674

Exhibit 5 to NS's Response to Sarepta's MIL No. 1

THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (GBW) [redacted]
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC. Plaintiff/Counter-Defendants.	

OPENING EXPERT REPORT OF STEVEN F. DOWDY, Ph.D.

[redacted]

462. Even beyond the microwalk, a POSA reading Popplewell 2010 would have been motivated to test an ASO that is 25 bases in length and 100% complementary to the (+36+60) region of human exon 53. For example, the claimed (+36+60) target region is immediately adjacent to the (+35+59) target region of PMO-A, shifted by just one base to the 3′ direction. As summarized above, Popplewell 2010 identified PMO-A (+35+59) as a viable clinical candidate. *See supra* § X.B.1.a; Popplewell 2010, 109. PMO-A also showed the highest skipping activity in hDMD mice. *See supra* § X.B.1.a; Popplewell, 2010, Figure 5. A POSA would have been motivated to move the target region for PMO-A in the 5′ and 3′ directions along human exon 53 within the highly active (+30+65) region taught by Popplewell 2010, which would have resulted in an ASO that is 25 bases in length and 100% complementary to the (+36+60) region of human exon 53. A POSA would have been motivated to move in both the 5′ and 3′ directions in part because the entire region is subsumed by other Type I PMOs, such as PMO-G (targeting the (+30+59) region), PMO-H (targeting the (+33+62) region) and PMO-I (targeting the (+35+65) region). As shown below, the difference between the target region for PMO-A (taught in Popplewell 2010) and the target region for the claimed ASO in the ’217 Patent is just *one* base.

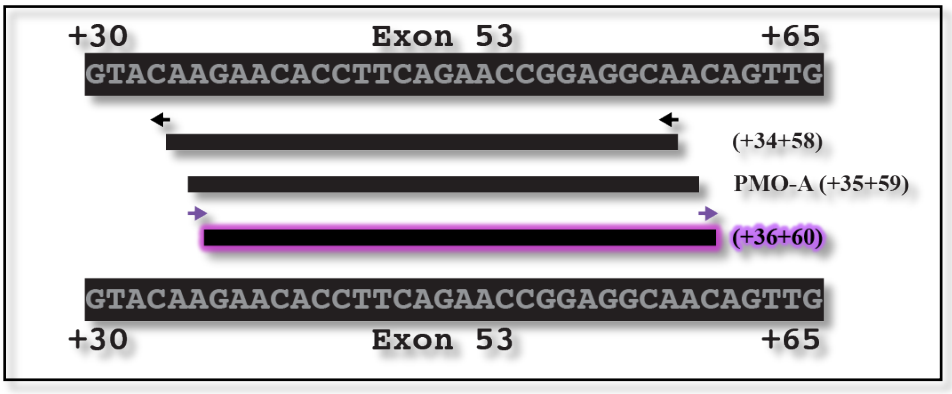


Figure 43. Modification of PMO-A

463. Whether using a conventional microwalk or moving the target regions for the clinical candidates taught in Popplewell 2010, a POSA reading Popplewell 2010 would have been

[redacted]

DATE: September 7, 2023

By: _____
Steven F. Dowdy, Ph.D.

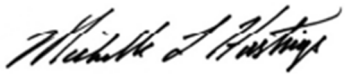
Exhibit 6 to NS's Response to Sarepta's MIL No. 1

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, **v.** **SAREPTA THERAPEUTICS, INC., Defendant.**	**C.A. No. 21-1015 (GBW)**
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant and Counter-Plaintiff **v.** **NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC., Plaintiff and Counter-Defendants.**	

RESPONSIVE EXPERT REPORT OF DR. MICHELLE L. HASTINGS REGARDING THE VALIDITY OF THE NS PATENTS

October 11, 2023



Michelle L. Hastings, Ph.D.

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c. Sarepta's arguments during prosecution of its '533 application contradict Dr. Dowdy's opinion that a POSA would have selected a 25-mer PMO

192. Sarepta's arguments during prosecution of its own application (14/776,533), in which Sarepta sought allowance of claims directed to a ***25-mer PMO targeting the +36+60 sequence in exon 53 with a TEG moiety at the 5' end***, support my opinion that a POSA would have focused on 30-mer PMOs over 25-mer PMOs. Specifically, during prosecution, the Examiner rejected Sarepta's claims as obvious over the combination of '212 Popplewell and U.S. 2013/0211062 ("Watanabe")[17]. 14/776,533 file history, Feb. 28, 2017 Office Action at 5. In response to the Examiner's argument that it would have been obvious to "incorporate Watanabe's PMO oligonucleotide [5'-TEG] structure into Popplewell's 25-mer within SEQ ID NO: 22 [a 30-mer]" (*id.* at 5-6), Sarepta argued that "[t]he Office did not, however, provide a reason why the skilled artisan ***would shorten the 30-base sequence of a PMO … to the 25-base sequence proposed by the Office***." 14/776,533 file history, Aug. 28,2017 Response at 19 (emphasis added).

193. In particular, Sarepta argued that "the skilled artisan would [have chosen] one of the ***more active compounds*** disclosed by ['212 Popplewell]." 14/776,533 file history, 8-28-2017 Response at 23. Sarepta explained that the '212 Publication "teaches that ***PMO-G … was superior to all the tested molecules that caused skipping of exon 53***," (emphasis added) and further noted that PMO-G "represent[ed] at the [] time, the optimal sequence for clinical trials in DMD boys." *Id*. And with respect to PMO-A specifically, Sarepta stated that it "produced little to no skipping." *Id.* at 27 (referring to h53A1 in '212 Popplewell's Table 1, which reports the same exon 53 skipping data as Popplewell 2010's Table 1) (emphasis added).

[17] I understand that Watanabe is the publication of a parent application to the NS Patents.

194. Sarepta continued stating that "[i]n fact, a skilled artisan ***did in fact choose h53A30/1 [PMO-G] as a lead compound***." *Id.* at 23. Sarepta explained:

> Watanabe [i.e., the NS Patents] prepared 16 different PMO compounds directed to exon 53. Watanabe at Table 2. Of note, PMO-12 and PMO-15 are described as "corresponding to h53A30/1 (cf. Table 1) in Non-Patent Document 5 …." *Id.* Watanabe defines "Non-Patent Document 5" as Linda J. Popplewell et al., (2010) Neuromuscular Disorders, vol. 20, no. 2, p. 102-10. … Applicants note that "h53A30/1" of Non-Patent Document 5 is the same "h53A30/1" of Popplewell. Popplewell at Tables 1 and 4 (indicating that h53A30/1 is 30 bases in length and has a start position at +33 (sic) of exon 53, and an end position of +59) and Non-Patent Document 5 at Table 1 (indicating that h53A30/1 is 30 bases in length and has a start position at +33 (sic) of exon 53, and an end position of +59). ***Thus, a skilled artisan actually selected PMO-G (h53A30/1) from all the possible molecules of Popplewell ….***

Id. (emphasis added).

195. After the Examiner maintained the rejection in the next office action, Sarepta argued that "Popplewell ***teaches away*** from shortening the 30-mer of SEQ ID NO:22 to a 25-mer" because "Popplewell states that '[o]ne of the parameters with high significance was length; ***30mer PMOs were far superior to their 25mer counterparts***." Dec. 14, 2018 Response at 24 (emphasis added). Sarepta explained that "while some 25-mers show efficient skipping at high concentration of 300 nM, ***only the 30-mers PMO-G and PMO-H show efficient skipping at reduced concentrations down to 25 nM***." *Id.* (emphasis added) Thus, according to Sarepta, "***Popplewell teaches very directly" that "a 25-mer would be expected to be significantly worse at exon 53 skipping***" and "[a]s such, Popplewell teaches away from" 25-mer PMOs. *Id.*[18] (emphasis added).

[18] Dr. Dowdy also argues that "[o]ther considerations would have motivated a POSA to select an array of 25-mer ASOs." Dowdy Report ¶ 456. For example, Dr. Dowdy states that "[l]onger ASOs are also at increased risk of hitting off-target genes due to their higher Tm and thereby ability to tolerate mismatched nucleotides." *Id.* But others in the field have in fact proposed that longer sequences are ***less likely*** to cause off-target effects. For example, in U.S. Patent No. 11,142,767,

Sazani at Figure 1.

198. In my opinion, the fact that ***AVI-4658 is a 30-mer PMO***, and was, at the priority date of the NS Patents, "***the only exon skipping PMO that was then in clinical trials***" (Dowdy Report ¶ 736 (emphasis added)), would have provided a POSA with yet another reason to pursue a ***30-mer PMO*** for clinical development.

3. Even if a POSA Would Have Selected PMO-A, They Would Not Have Modified it as Suggested by Dr. Dowdy

199. Even assuming that a POSA would have considered PMO-A as a lead candidate to modify, they would not have been motivated to modify PMO-A to arrive at the claimed PMO. As even Sarepta argued during prosecution of its '533 application, "Popplewell's approach … provides ***no indication*** as to what parameters are critical for the design of exon skipping antisense. As each antisense oligonucleotide must be tested, the results are ***unpredictable*** as indicated by the results in Popplewell." Aug. 28, 2017 Response at 26 (emphasis added). As Sarepta has further acknowledged, "changing the … target coordinates of an antisense oligonucleotide in either the ***5' or 3' direction is not predictable***." *Id*. at 27 (emphasis added).

200. Given this, there is nothing in Popplewell that would have motivated a POSA to shift the target coordinates of PMO-A in the 3' direction, as Dr. Dowdy suggests, and Dr. Dowdy fails to point to any evidence supporting his assertion that a POSA would have been motivated to do so. Indeed, Popplewell leads a POSA away from Dr. Dowdy's proposed modification because, of the 25-mers tested in Popplewell, while PMO-A had a poor efficiency of only 12.7%, PMO-B (which is shifted three nucleotides in the 3' direction from PMO-A) had an even worse efficiency of 9.7%. Popplewell at Table 1. The same is true for the data presented in Figure 1b. The illustration below helps visualize this trend:

glycol chain…." *Id.* at 25 (emphasis added). Therefore, Wilton 2011 discloses conjugating a PMO with a polyethylene glycol moiety.[27]

2. Sazani's Safety Data

255. Dr. Dowdy states that "Sazani 2010 also provided detailed safety and genotoxicity information that was not otherwise available." Dowdy Report ¶ 737. Dr. Dowdy, however, does not rely on Sazani's genotoxicity data in any substantive way. Dr. Dowdy's obviousness section mentions "genotoxicity" 15 times and "genotoxic" 7 times, but in each of these instances, Dr. Dowdy merely quotes from or summarizes Sazani. Dr. Dowdy never provides a discussion as to ***how or why*** the genotoxicity data of Sazani would have been important information to a POSA looking to use a PMO with 5'-TEG modification. In fact, Dr. Dowdy appears to only rely on Sazani's genotoxicity data to conclude that "Sazani 2010 demonstrated that the combination of a PMO backbone and 5′-TEG modification ***could be safely administered***." *Id.* (emphasis added). As shown below, this was already disclosed in 2010 Popplewell.

256. As disclosed in 2010 Popplewell:

> ***Initial proof-of-principle clinical trials***, using two different AO chemistries (phosphorothioate-linked 2'-O-methyl modified bases (2'OMePs) [14] and ***phosphorodiamidate morpholino oligomer (PMO) [15])*** for the targeted skipping of exon 51 of the *DMD* gene after intramuscular injection, have been performed recently with encouraging results. While both chemistries ***have excellent safety profiles*** [***16***,17], PMOs appear to produce more consistent and

[27] I note that the specification of the NS Patents also discuss the teachings of WO 2009/064471, which Dr. Dowdy refers to as "Reeves PCT '471." The applicant of Reeves PCT '471 is AVI BioPharma. Dr. Dowdy states that "[i]n Examples 5 and 6, for example, Reeves PCT '471 reports that ***an exemplary PMO with a particular 5'-end modification known as a triethylene glycol ("TEG") modification*** (sometimes referred to the TEG tail) was made …." Dowdy Report ¶ 112 (emphasis added); *see also id.* ¶ 436 ("Reeves PCT '471 discloses that this method can be used to make a ***PMO with a TEG modification at its 5'-end***." (emphasis added)). Thus, in addition to the five "References Cited" discussed above, the specification of the NS Patents disclose yet an additional reference that provides teachings that are cumulative to Sazani's.

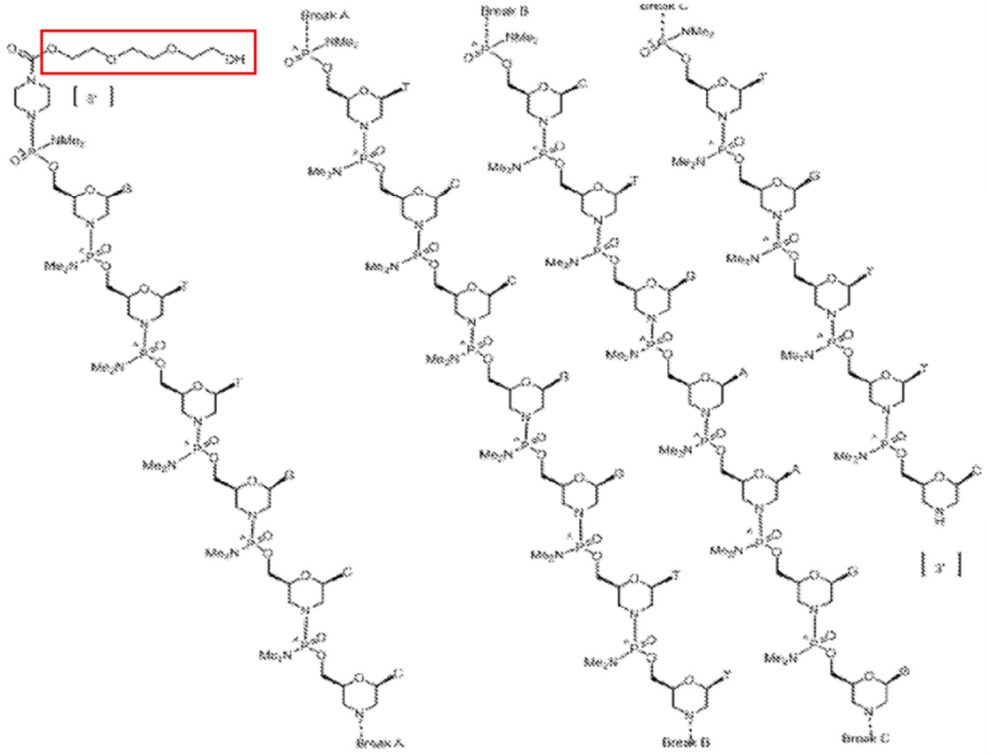
[redacted]

2004 publication date, AVI Biopharma had multiple PMOs in human clinical trials (*id.* at Table 3), indicating that PMOs were sufficiently safe for human administration.

3. Sarepta Did Not View Sazani as Relevant to Its Own Applications Directed to a PMO Having a 5'-TEG Modification

261. As noted above, Sarepta's '533 application, filed in 2013, sought allowance of claims directed to a ***PMO having a 5'-TEG modification***. I have illustrated the claim below:

16. **(Original)** An antisense oligomer, wherein the oligomer has a structure selected from the group consisting of:



H53A(+36+60),

14/776,533 file history, 2-29-2016 Claims. As highlighted above, the claimed PMO also targeted positions +36+60 of exon 53. Thus, the claims of the '533 application were directed to ***subject***

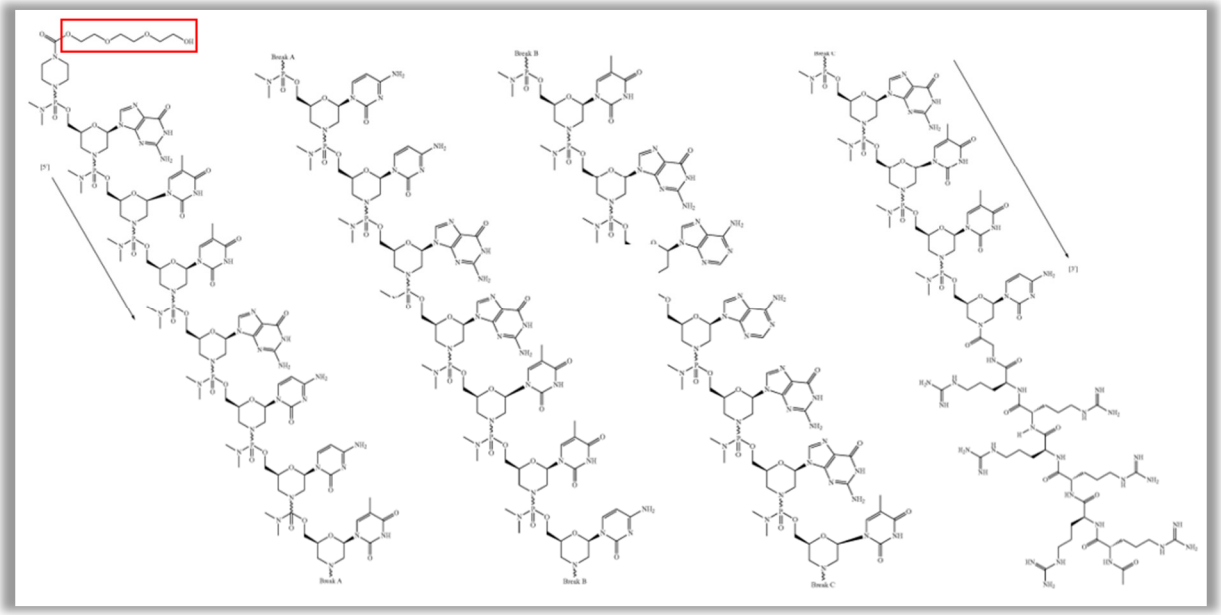
[redacted]

matter that is identical to many claims of the NS Patents, *i.e.*, those specifically claiming a PMO with a 5'-TEG modification.

262. I have reviewed the information disclosure statements that Sarepta submitted during prosecution of its '533 application.[29] Although Sarepta submitted ***over one thousand references***, including Popplewell 2009, Popplewell 2010, '212 Popplewell, Kinali and '591 Sazani, ***Sarepta did not submit the Sazani paper***.

263. I understand that Sarepta's U.S. Patent No. 11,000,600 claims a method of using a ***PMO targeting positions +36+60 of exon 53*** of the human dystrophin pre-mRNA conjugated with a ***TEG at its 5' end***. Specifically, claim 1 of the '600 patent recites "[a] method of treating Duchenne muscular dystrophy (DMD) in a primate subject… comprising administering the primate subject an antisense oligomer conjugate of Formula (IV)." The oligomer of Formula (IV) has the following structure:

[29] I understand that an information disclosure statement (also known as an IDS) is a document submitted to the USPTO identifying the prior art (e.g., patents, publications, non-patent literature) and other relevant information that an applicant is aware of. I am informed that the purpose of the IDS is to satisfy the duty of candor and good faith in dealing with the USPTO.



'600 Patent at Claim 1. As is clear, the claimed structure is a ***PMO with a TEG modification at its 5' end***. I have reviewed the "References Cited" from the '600 patent and did not identify the Sazani paper from that list. I also did not identify the Sazani paper in the "References Cited" for U.S. 11,395,855, which is a continuation of the '600 patent, and claims "[a]n antisense oligomer conjugate of Formula (IV)," *i.e.*, a ***PMO with a TEG modification at its 5' end***.

264. That Sarepta did not view the Sazani paper as relevant to the claims of its '533 application, '600 patent or '855 patent lends further support and confirmation of my opinion that Sazani is cumulative to the references discussed above.

XII. ADDITIONAL EVIDENCE SUPPORTING MY OPINION THAT THE UWA PATENTS DO NOT DEFINE A 'HOT-SPOT' AMENABLE TO EXON-SKIPPING SPANNING POSITIONS +23 TO +69 OF EXON 53

265. Additional post-priority date evidence supports that Dr. Wilton and his co-inventors neither recognized nor appreciated the +23 to +69 region of exon 53 to be a "hotspot" as of the June 28, 2005 filing date of PCT/AU2004/000943, published as WO 2006/000057 ("Wilton 2005 PCT"). Dr. Fletcher, a named co-inventor of the UWA Patents testified that the region amenable

Exhibit 7 to NS's Response to Sarepta's MIL No. 1

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff,	)	
v.	)	**C.A. No. 21-1015 (GBW)**
SAREPTA THERAPEUTICS, INC., Defendant.	)	
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant and Counter-Plaintiff	)	
v.	)	
NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC., Plaintiff and Counter-Defendants.	)	

REPLY EXPERT REPORT OF DR. MICHELLE L. HASTINGS REGARDING THE INVALIDITY OF THE UWA PATENTS

October 27, 2023

Michelle L. Hastings, Ph.D.

that the specification provides adequate written description support" for the asserted claims of the UWA Patents supports my opinion that ***no POSA, in 2005***, would have understood that the UWA Patents identified any kind of "hotspot" for exon 53 skipping.

58. Dr. Dowdy mentions two "Bestwick" PCTs as evidence purportedly "***confirming***" that the specification of the UWA Patents provides a sufficient written description. Dowdy Rebuttal ¶ 85. The continued prosecution of one of those applications, PCT/US2013/077216 (which published as WO 2014/100714), is worth discussing. PCT/US2013/077216 was filed on December 20, 2013. A continuation application (14/743,856), claiming priority to PCT/US2013/077216, was filed on June 18, 2015. Sarepta filed a continuation application (15/420,823) on January 3, 2017 and filed a preliminary amendment on September 14, 2017, with claims directed to:

> 1. An isolated an antisense oligonucleotide of 20 to 50 nucleotides in length comprising at least 20 consecutive nucleotides to an exon 53 target region of the dystrophin gene designated as an annealing site H53A(+33+60), wherein the oligonucleotide comprises a non-natural backbone and specifically hybridizes to an exon 53 target region of the Dystrophin gene and induces exon 53 skipping.

U.S. Application No. 15/420,823 file history, Sept. 14, 2017 Claims.

59. The Examiner issued an Office Action on April 6, 2018, rejecting the claims as anticipated by "Wilton et al. (WO 2011/057350 A1)," *i.e.*, "Wilton PCT '350." *Id.*, Apr. 6, 2018 Office Action at 5. The Examiner stated:

> Wilton et al. teach exon 53 skipping using antisense molecule H53A(+33+65) (Figure 43, page 11, page 13). The sequence on page 13 is 33 nucleotides in length and (SEQ ID NO: 59) comprises instant SEQ ID NO: 1. … Therefore, the claims are anticipated by Wilton et al.

Id. at 7.

60. Sarepta responded to the Office Action on August 6, 2018, and amended the claims as follows:

> 1. An isolated an antisense oligonucleotide of ~~20 to 50~~ 21 nucleotides in length comprising at least 20 consecutive nucleotides to an exon 53 target region of the dystrophin gene designated as an annealing site H53A(+33+60), wherein the oligonucleotide comprises a non-natural backbone and specifically hybridizes to an exon 53 target region of the Dystrophin gene and induces exon 53 skipping.

Id., Aug. 6, 2018 Response at 2. In the response, Sarepta argued:

> The Office cites SEQ ID NO: 59 of Wilton, which is 33 nucleotides in length. Office Action at 7. ***Independent claims 1 and 24 are amended to recite an antisense oligonucleotide of 21 nucleotides*** in length. Thus, ***Wilton does not teach all of the elements of the claims*** and the anticipation rejection over Wilton should be withdrawn.

Id. at 5-6.[25] The Examiner was persuaded by this argument and withdrew the anticipation rejection. *Id.*, Nov. 7, 2018 Office Action at 3-9.

61. It appears that Sarepta was attempting to capture NS's product viltolarsen, which is a 21-mer PMO targeting positions +36+56 of human exon 53. But if, according to Sarepta, "Wilton [PCT '350] does not teach all of the elements" of viltolarsen, how can Sarepta assert that

[25] The Examiner had also rejected the claims over WO 2010/0458586, *i.e.*, Dr. Dowdy's "Sazani PCT '586." Sarepta responded by stating that "SEQ ID NO: 631 of Sazani [] is 30 nucleotides in length" (*id.* at 5), and because the claims were "amended to recite an antisense oligonucleotide of 21 nucleotides in length… the anticipation rejection over Sazani should be withdrawn." *Id.* SEQ ID NO: 631 is H53A(+32+61) (5'-TGTTGCCTCCGGTTCTGAAGGTGTTCTTGT-3'). If H53A(+32+61) does not anticipate an AO "of 21 nucleotides in length comprising at least 20 consecutive nucleotides to an exon 53 target region of the dystrophin gene designated as an annealing site H53A(+33+60)," how can Popplewell's SEQ ID NOs: 10-12 "corresponding respectively to the (+33+62), (+36+65), and (+30+59) regions of exon 53" and "[c]ollectively … span[ning] the narrower (+30+65) region" anticipate NS's claimed AO consisting of 25 nucleotides in length and targeting positions +36+60 of exon 53?

the UWA Patents contain a written description that a POSA would understand discloses viltolarsen? Per Dr. Dowdy's own admission, Wilton PCT '350 "further confirmed [the Wilton] group's earlier discovery of the exon 53 hot spot" by "disclos[ing] more than 20 ASOs targeting human exon 53 … many of [which] fell within or overlapped with the previously-identified hot spot and induced exon skipping." Dowdy Opening ¶ 105; *see also* Dowdy Rebuttal Tables 15 and 16 (listing H53A(+27+56) and H53A(+33+63) from Wilton PCT '350 as falling within the scope of the UWA Patent claims).

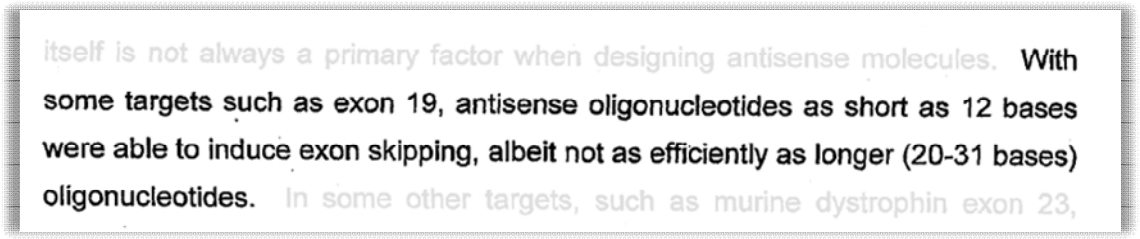
62. Indeed, Wilton PCT '350 discloses all of the "claimed structural features that" Dr. Dowdy states "correlate the claimed function of exon 53 skipping." Dowdy Rebuttal ¶ 74. For example, Table 43 of Wilton PCT '350 discloses many AOs that induced exon 53 skipping. In particular, to use Dr. Dowdy's own words, a group of AOs (in green) "is reported to induce exon skipping and defines one end of the hot spot." Dowdy Rebuttal ¶ 74. Another group of AOs (in blue) "is also reported to induce exon skipping and defines the other end of the hot spot." *Id.*

H53A(+39+65)	CAA CUG UUG CCU CCG GUU CUG AAG GUG	skippping 50 nM
H53A(+39+67)	UUC AAC UGU UGC CUC CGG UUC UGA AGG UG	skippping 100 nM
H39A(+39+69)SNP	CGU UCA ACU GUU GCC UCC GGU UCU GAA GGU G	skipping to 25 nM
H53A(+40+70)	UCA UUC AAC UGU UGC CUC CGG UUC UGA AGG U	skippping 50 nM
H53A(+41+69)	CAU UCA ACU GUU GCC UCC GGU UCU GAA GG	skippping 50 nM
H53A(+43+69)	CAU UCA ACU GUU GCC UCC GGU UCU GAA	skippping 50 nM
H53A(+69+98)	CAG CCA UUG UGU UGA AUC CUU UAA CAU UUC	Skipping at 50 nM
Hint52(-47-23)	UAU AUA GUA GUA AAU GCU AGU CUG G	No skipping
H53A(+27+56)	CCU CCG GUU CUG AAG GUG UUC UUG UAC UUC	strong skipping to 25 nM faint at 5 nM
H53A(+27+59)	UUG CCU CCG GUU CUG AAG GUG UUC UUG UAC UUC	strong skipping to 10 nM faint at 5 nM
H53A(+30+59)	UUG CCU CCG GUU CUG AAG GUG UUC UUG UAC	
H53A(+30+64)	AAC UGU UGC CUC CGG UUC UGA AGG UGU UCU UGU AC	strong skipping to 25 nM faint at 10 nM

Wilton PCT '350 at Table 43. It also discloses an AO comprising a "at least 12 consecutive bases of [SEQ ID NO: 195]," *e.g.*, H53A(+27+56) and H53A(+27+59).

63. Wilton PCT '350 also discloses the very passage that Dr. Dowdy states "explains that for some exons, an ASO having 12 consecutive bases to a target region may be sufficient to

induce exon skipping but would be more efficient if those bases are present in the context of a longer ASO, i.e., 20-31 bases in length." Dowdy Rebuttal ¶ 74.



itself is not always a primary factor when designing antisense molecules. With some targets such as exon 19, antisense oligonucleotides as short as 12 bases were able to induce exon skipping, albeit not as efficiently as longer (20-31 bases) oligonucleotides. In some other targets, such as murine dystrophin exon 23,

Wilton PCT '350 at 17:17-20.

64. In sum, Wilton PCT '350 discloses all of the relevant "structural features" that Dr. Dowdy asserts "correlate the claimed function of exon 53 skipping." Dowdy Rebuttal ¶ 74. Yet, Sarepta asserted during prosecution of its U.S. Application No. 15/420,823 that Wilton PCT '350 "does not teach all of the elements" of viltolarsen, which is a 21-mer PMO targeting +36+56. In my opinion, this is fatal to Sarepta's argument that the UWA Patents, which certainly do not disclose more information than Wilton PCT '350, contain a sufficient disclosure such that a POSA would understand that they disclose Dr. Dowdy's "universe" of PMOs, including viltolarsen.

65. Finally, Dr. Dowdy states that I "completely ignore[] the direct evidence available in this case, reflecting what a POSA would have understood from reading the specification," including "[f]irst and foremost" that "researchers at Sarepta recognized long before this litigation that the Wilton Patents disclosed an 'effective target region of +23 to +69 relative to the splice acceptor site.'" Dowdy Rebuttal ¶ 134 (citing the Sarepta Sequence Selection Report). I note that it is not immediately apparent whether the section of the Sequence Selection Report that Dr. Dowdy relies on, titled "Overview of Exon 53 Screens from Research and Patent Literature" (SRPT-VYDS-0201529), was drafted by "researchers at Sarepta" or by a patent attorney prosecuting the applications that eventually issued as the UWA Patents. *See, e.g.*, Naughton

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH)
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC. Plaintiff/Counter-Defendants.	

SAREPTA THERAPEUTICS, INC. AND THE UNIVERSITY OF WESTERN AUSTRALIA'S REPLY IN SUPPORT OF MOTION *IN LIMINE* NO. 1 TO EXCLUDE EVIDENCE OR ARGUMENT REGARDING OTHER PROCEEDINGS INVOLVING PATENTS NOT IN SUIT

NS does not address the significant prejudice and jury confusion that would result if allowed to present on satellite proceedings involving other Sarepta and UWA patents. Those patents have different priority dates, disclosures, and/or claims, and should be excluded. *Sonos*, 2017 WL 5633204, at *1.

NS argues that Sarepta's patent attorney in the Species Cases argued patentability over Popplewell in seeking its own claims to the 25-mer PMO claimed in the NS Patents, accusing Sarepta of presenting inconsistent arguments here. Br. 2. But NS ignores the key points: the PTO ***rejected*** Sarepta's arguments there, ***maintained*** its §103 rejections, and Sarepta ***abandoned*** the Species Cases. Ex. B. Reference to abandoned arguments from an unrelated application would be irrelevant and prejudicial. *Solvay*, No. 06-557-SLR, D.I. 329 at 1-2 (excluding prosecution files that characterized common prior art from unrelated and related abandoned applications).[1]

NS next argues that Sarepta's non-submission of Sazani 2010 during prosecution of the Species and Sazani Cases shows that it is cumulative. Br. 3. But these cases involved different priority dates and different submitted references than the NS Patents—Sazani 2010 is not even prior art to the Sazani Cases. Ex. C, ¶ 184. NS also argues that attorney arguments made during the '007 Interference should be admissible "facts" because the resulting decision was cited during prosecution of the Wilton '851 Patent. Br. 1-2. NS's out-of-context use of these arguments would require time-consuming explanation of interference practice and the different standards of proof.

Finally, the case NS relies on states only that a patentee's representations "during the prosecution of its patent application" are binding "during subsequent litigation ***over the [same] patent***." *Procter*, 711 F. Supp. at 770. The Species Cases, the Sazani Cases, and the '007 Interference involve ***different*** patents. *Procter* does not apply.

[1] While NS's satellite arguments should be excluded, if permitted, the jury would need to be told the PTO ***confirmed*** that the claims were obvious over Popplewell, as Sarepta contends here.

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April 29, 2024

CERTIFICATE OF SERVICE

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VIA ELECTRONIC MAIL

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EXHIBIT B

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/776,533	09/14/2015	Richard K. BESTWICK	AVN-017CPUS	2035

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Nelson Mullins Riley & Scarborough LLP/Sarepta
One Post Office Square
Boston, MA 02109

EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1674	

NOTIFICATION DATE	DELIVERY MODE
11/16/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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ipqualityassuranceboston@nelsonmullins.com

Office Action Summary	Application No. 14/776,533	Applicant(s) BESTWICK et al.	
	Examiner DANA H SHIN	Art Unit 1674	AIA Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 28 August 2017

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☑ Claim(s) 16–17 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☑ Claim(s) 16–17 is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____ .

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____ .

4) ☐ Other: _____ .

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on August 28, 2017.

Currently, claims 16-17 are pending and under examination on the merits in the instant application.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Information Disclosure Statement

Applicant's representative commented over the phone that one IDS was not considered by the examiner. The examiner was unable to identify an unconsidered IDS. Applicant is advised to specifically address/communicate the unconsidered IDS in writing by providing the image of the first page of the unconsidered IDS. Upon verification that the IDS was indeed not considered, the examiner will consider the IDS and mail the considered IDS.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

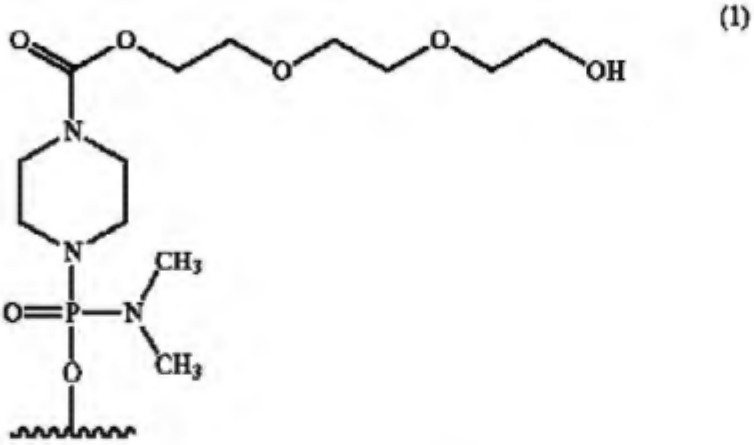
Claim Rejections - 35 USC § 102

Claims 16-17 remain rejected under 35 U.S.C. 102(e) as being anticipated by Watanabe et al. for the reasons of record as set forth in the Office action mailed on February 28, 2017 and for the reasons set forth below.

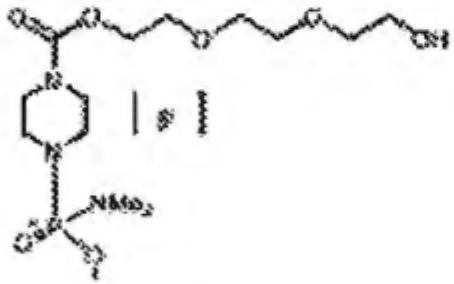
Applicant's arguments filed on August 28, 2017 have been fully considered but they are not persuasive. Applicant argues that Watanabe does not "explicitly" disclose the structure claimed in the instant case. Applicant then compares Watanabe's 2'-O-methyl AON structure to the claimed PMO structure to show structural differences. In response, it is noted that the instant rejection is not based on Watanabe's 2'-O-methyl structure. Now, note that the anticipation does not require actual performance or actual compound to be "explicitly" disclosed. The fact remains that Watanabe "explicitly" disclosed the instantly claimed PMO structure (see formula (I)) as well as the 5' PEG conjugate structure (see Group (1)). It is true that the instantly claimed nucleotide sequence is expressly exemplified only as a 2'-O-methyl RNA oligonucleotide by Watanabe. However, the Watanabe publication expressly taught that exon-skipping oligonucleotide can be a 2'-O-methyl RNA oligonucleotide or PMO DNA oligonucleotide. As such, one of ordinary skill in the relevant art fully reading and understanding the teachings of the Watanabe reference would at once envisage and readily draw a 5'-PEG conjugated PMO structure having the claimed DNA sequence.

"**If one of ordinary skill in the art is able to "at once envisage" the specific compound** within the generic chemical formula, **the compound is anticipated**. One of ordinary skill in the art **must be able to draw** the structural formula or write the name of each of the compounds included in the generic formula before any of the compounds can be "at once envisaged."" (emphasis added). See MPEP §2131.02.

Applicant argues that Watanabe's 5' PEG is "being fixed as hydroxyl" thus does not teach that the 5' end is "variable." The examiner fails to understand applicant's argument. The 5' end of the PMO antisense oligomer having formula (I) is disclosed as following in paragraph 0162 of Watanabe:



Now, compare the above structure to the instantly claimed 5' end as directly copied from the fuzzy structure as submitted in the claims by applicant:



As far as the examiner can see, there is no structural difference between the two 5' terminal PEG moieties conjugated to the 5' end of the PMO unit, unless the examiner is missing a structural element in the fuzzy structure in the claims.

Applicant then goes over Watanabe's paragraphs 0021 and 0082 to attack that Watanabe disclosed various target regions/lengths and "a long laundry list of possible nucleobases". The examiner fails to understand the relevance of applicant's arguments. The instant anticipation rejection is based on the explicitly disclosed exon 53 skipping nucleotide sequence, which is SEQ ID NO:57 thus the mere fact that Watanabe disclosed other target regions/lengths and

nucleobases does not show that the claimed nucleotide sequence having PMO units and a 5' terminal PEG conjugate is not taught by Watanabe's reference.

In view of the foregoing, this rejection is maintained.

Claim Rejections - 35 USC § 103

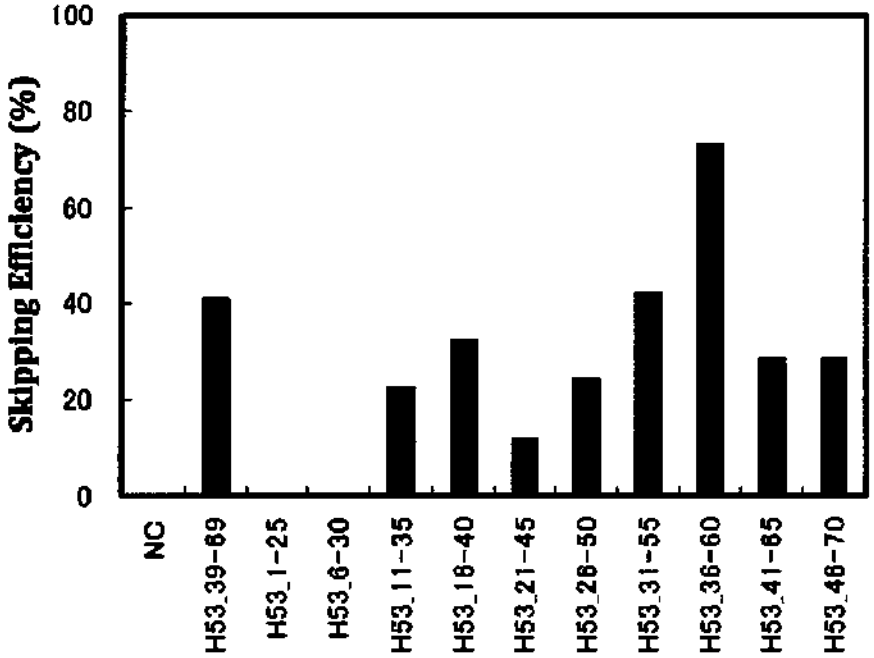
Claims 16-17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Watanabe et al. for the reasons of record as set forth in the Office action mailed on February 28, 2017 and for the reasons set forth below.

Applicant's arguments filed on August 28, 2017 have been fully considered but they are not persuasive. Applicant argues that the examiner failed to provide a reason as to why one of ordinary skill in the art would have selected Watanabe's H53_36-60 as a "lead compound" with a reasonable expectation of success. In particular, Applicant points out the Otsuka case (Fed. Cir. 2012) and argues that a compound cannot be a lead compound when other compounds having "higher activity" are available. In response, it is noted that there is no *per se* rule that requires a selection of a single lead compound for obviousness under §103. See MPEP §2143: The Federal Circuit in *Eisai* makes it clear that from the perspective of the law of obviousness, **any known compound might possibly serve as a lead compound…**It should be noted that the **lead compound cases do not stand for the proposition that identification of a single lead compound is necessary in every obviousness rejection of a chemical compound**." (emphasis added). Further, applicant did not point out how the Otsuka case (Fed. Cir. 2012) is relevant and analogous to the instant rejection. Note that in *Otsuka*, the claims at issue pertain to an antipsychotic compound and the Courts have determined that one of ordinary skill in the art would not have selected the prior art "OPC-4392" compound for modification because the prior art compound "did **not** treat positive symptoms of schizophrenia" thus the prior art compound "was viewed as **lacking "antipsychotic component**", and furthermore, the prior art compound

"was likely to **cause patients to act out their delusions and hallucinations**", thereby aggravating psychotic symptoms hence has pro-psychotic, not anti-psychotic, activity. Hence, both the district court and the Federal Circuit found that "the prior art **taught away** from using OPC-4392 as a starting point for further antipsychotic research." (emphasis added). In the instant case, there is no teaching in Watanabe that SEQ ID NO:57 cannot have a PMO modification or that SEQ ID NO:57 lacks exon 53 skipping activity. That is, Watanabe does not provide any disclosure that teaches away from using the 25-mer sequence as an exon 53 skipping oligonucleotide modified with PMO and a 5'-PEG conjugate. As such, there is no analogy/similarity between the fact pattern of the instant case and that of the Otsuka case. As such, the examiner finds applicant's heavy reliance on the Otsuka case irrelevant and unpersuasive.

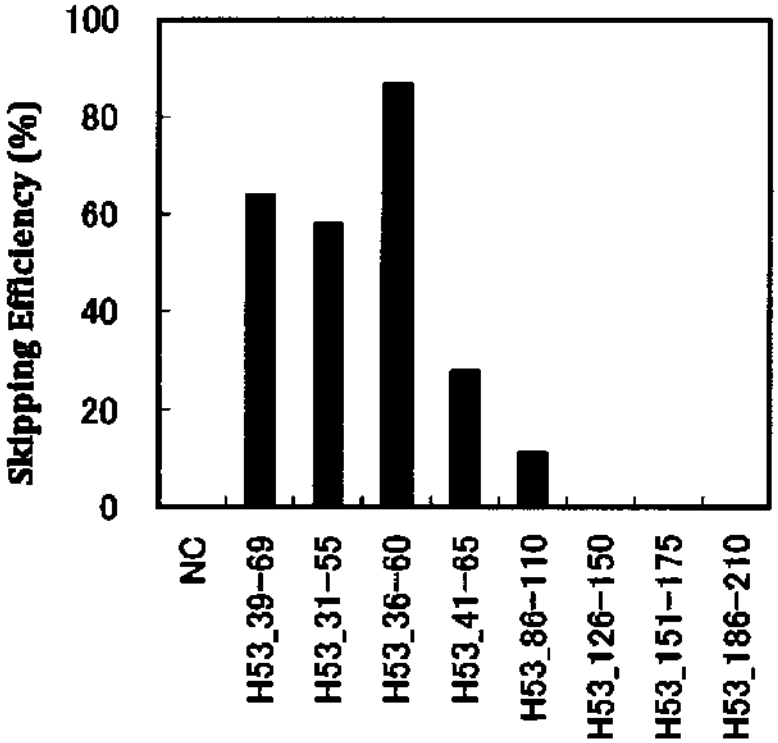
In fact, in stark contrast to the "OPC-4392" prior art compound that was deemed unsuitable as a compound to be selected for further modification in *Otsuka* since it displayed pro-psychotic properties instead of anti-psychotic properties, Watanabe's SEQ ID NO:57 ("H53_36-60") showed one of the greatest exon 53 skipping efficiency at about 80%-90% compared to other oligonucleotides. Hence, Watanabe's SEQ ID NO:57 was one of oligonucleotides having "higher activity" therefore applicant's argument that a compound cannot be a lead compound when other compounds having "higher activity" are available is not found persuasive. See Watanabe's Figure 9 as copied below:

Figure 9



See also Figure 13 demonstrating that SEQ ID NO:57 showed the highest level of exon 53 skipping efficiency:

Figure 13

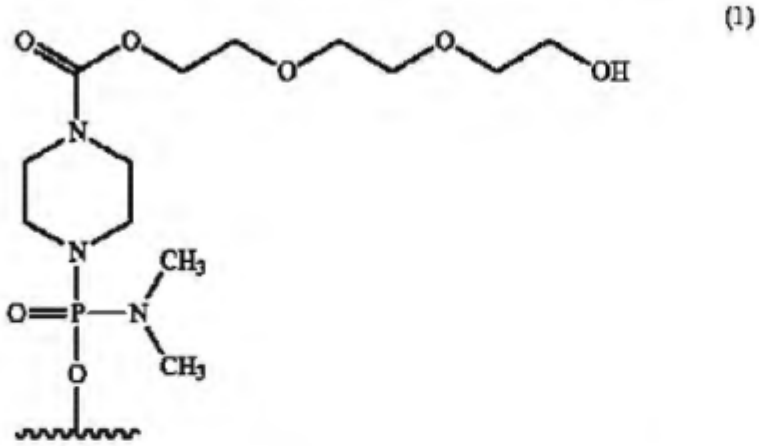


In view of the foregoing, the examiner finds applicant's arguments made in comparison to the Otsuka case completely unpersuasive and the examiner fails to understand why the non-analogous Otsuka case that is repeatedly mentioned and addressed throughout the remarks should be even considered in the instant case. It is noted that all of applicant's arguments pertaining to the Otsuka case bear no merit whatsoever for the reasons stated hereinabove.

Further, in view of the expressly demonstrated efficient exon 53 skipping activity pertaining to Watanabe's SEQ ID NO:57 ("H53_36-60"), applicant's arguments addressing "unpredictable" AON activity thus lack of reasonable expectation of success by further pointing out various documents at pages 16-18 of the remarks are found unpersuasive and irrelevant. Note that the documents pointed out by applicant cannot rebut or nullify the results obtained by Watanabe's SEQ ID NO:57 ("H53_36-60") as illustrated in the above Figures thus there is no objective, factual evidence that supports applicant's alleged high level of unpredictability and lack of reasonable expectation of success pertaining to an oligonucleotide targeted to "H53_36-60".

Applicant argues that there is no reason/motivation to select Watanabe's SEQ ID NO:57 as a lead compound. Again, there is no legal requirement tbat a selection of a "lead compound" is necessary for §103. The fact remains that Watanabe's antisense oligonucleotide targeted to human dystrophin exon 53 at positions 36-60 (SEQ ID NO:57) was expressly disclosed as one of a finite number of efficient exon 53 skipping oligonucleotides. As such, any one of Watanabe's efficient oligonucleotides including SEQ ID NO:57 was available to a person of ordinary skill in the art to make an exon 53 skipping oligonucleotide. In addition, Watanabe's SEQ ID NO:57 showed "higher activity" in exon 53 skipping as shown in Figures 9 and 13. As such, there is no sufficient reason not to select SEQ ID NO:57 for PMO and 5'-PEG conjugate modifications, wherein the two combination modifications were "identified, predictable solutions" available in the relevant art when making an exon skipping oligonucleotide as evidenced by Watanabe's

teaching of exon skipping oligonucleotides comprising both PMO and the 5' PEG conjugate structure as represented by chemical formula (1) claimed in claim 8 as copied below:



Applicant argues that Watanabe shows four oligonucleotides that are "more effective" than SEQ ID NO:57 by pointing out Figure 17 hence the four oligonucleotides "would have been more promising than" SEQ ID NO:57. In response, the mere fact that there are other oligonucleotides that provided more efficient exon 53 skipping than SEQ ID NO:57 does not whatsoever indicate that one of ordinary skill in the art was taught away or discouraged from using the very effective SEQ ID NO:57. The mere presence of other options does not render the instant claims nonobvious because any one of Watanabe's oligonucleotides shown to have exon 53 skipping activity (thus including SEQ ID NO:57 and four oligonucleotides that are more efficient than SEQ ID NO:57) would have been a natural compound to be selected when making an exon 53 skipping oligonucleotide modified with the well-known, art-recognized PMO and the 5'-PEG conjugate modifications. Put it differently, all of efficient oligonucleotides showing exon skipping activity in Figure 17 are suitable candidates for making a PMO oligonucleotide. Hence, one of ordinary skill in the art would have modified SEQ ID NO:57 as well as all other oligonucleotide having exon skipping efficiency, thereby rendering the claimed compound *prima facie* obvious.

Applicant argues even if Watanabe's SEQ ID NO:57 was selected, there is no reason or motivation to replace Watanabe's uracil with thymine. In response, applicant's attention is directed to the fact that the obviousness analysis utilizes a person of ordinary skill in the relevant art, not any layperson. It is *prima facie* obvious knowledge in the relevant art that PMO conventionally utilizes DNA bases as evidenced by Watanabe's teaching of making PMOs comprising SEQ ID NO:2-37 (see paragraphs 0026-0030), all of which are DNA sequences listed in Table 1. As such, there is no technical difficulty or unpredictability involved in utilizing a DNA sequence corresponding to Watanabe's RNA sequence of SEQ ID NO:57 when making a PMO.

Applicant argues that Watanabe does not teach replacing 2'-O-methyl modification in SEQ ID NO:57 with PMO. Contrary to applicant's argument, Wanatabe taught that DMD exon 53 skipping oligonucleotides can be in the form of a PMO or a 2'-O-methyl oligomer, thereby providing two chemical modification options when making a DMD exon 53 skipping oligonucleotide. Note that all of Watanabe's oligonucleotides either PMO-modified (see Figure 18) or 2'-O-methyl-modified (see paragraph 0286 and Figures 9 and 13). As such, Watanabe expressly taught only two possible exon skipping oligonucleotide formats: PMO and 2'-O-methyl. Further, the instantly claimed 5' PEG terminal conjugate is one of three 5' end structures (formulas (1)-(3) in claim 8) when making a PMO. Hence, one of ordinary skill in the art properly reading the Watanabe reference would readily understand that PMO and 2'-O-methyl are alternative oligonucleotide formats when making exon skipping oligonucleotides, and since there were only two identified exon skipping formats taught by Watanabe, who also taught three identified 5' end structures for a PMO, a person of ordinary skill in the art would have reasonably pursued making a 5'-PEG conjugated PMO as an obvious alternative approach when making a DMD exon 53 skipping oligonucleotide, wherein the person would have had

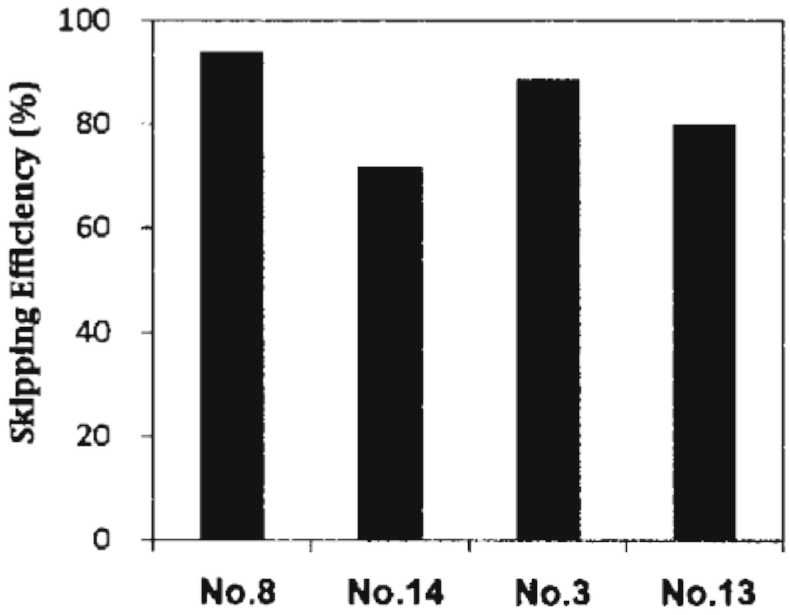
reasonably selected SEQ ID NO:57 because it demonstrated high exon skipping efficiency (about 80%-90%) as demonstrated in Figures 9, 13, and 17.

Applicant argues that there is no motivation to use Watanabe's Group (1), the PEG conjugate, because Watanabe indicated that Group (3) is "preferred" among Group (1), Group (2), and Group (3) by pointing out paragraph 0162, which states that "the 5' end may be any of chemical structures (1) to (3) below, and preferably is (3)-OH." In response, the phrase "preferably is (3)-OH" does not teach or suggest that Group (3) alone should be used when making exon skipping PMOs, nor does the phrase teach that Group (1) should not be used. It is clear from the disclosure in paragraph 0162 that Groups (1)-(3) are alternative structures as Watanabe teaches that the 5' end "may be **any** of chemical structures (1) to (3)". It becomes even clearer that the three 5' end structures are alternatives and "any" one of Groups (1)-(3) can be used when Watanabe's claim 8 that expressly recites "wherein the 5' end **is any one** of the groups of chemical formulae (1) to (3)" is taken into consideration. Note that there is no teaching in Watanabe that disparages use of Group (1), and if such were the case, Watanabe would not have claimed Group (1) as one of 5' end group. In addition, note that the mere word "preferably" does not teach away from using Group (1) thus does not render allegedly non-preferred compounds (e.g., Group (1) and Group (2)) nonobvious. See MPEP §2123: "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments."

Applicant argues that one of ordinary skill in the art would have selected Group (3) but not Group (1) by comparing PMOs 3 and 8 having Group (3) to PMOs 13 and 14 having Group (1) and by pointing out that other prior art used Group (3), not Group (1). Applicant goes even further to allege that the examiner's rejection based on the use of Group (1) "contradicts the teachings of Watanabe." Contrary to applicant's arguments and allegations, there is no sufficient reason that one of ordinary skill in the art would not select Group (1) as alleged by applicant

because PMOs 13 and 14 provided good/high levels (70-80%) of exon 53 skipping efficiency as clearly demonstrated in Figure 8 copied below:

Figure 8



There is nothing in Watanabe including paragraphs 0162 and 0313 pointed out by applicant that clearly criticizes or disparages use of Group (1) at the 5' end when making an exon 53 skipping PMO. Again, Watanabe expressly taught "any" one of Group (1), Group (2), and Group (3) "**is**" the 5' end group (see claim 8) and furthermore demonstrated that PMOs having Group (1) provided good/high levels (70-80%) of exon 53 skipping efficiency thus use of Group (1) was not discouraged by Watanabe's teachings. As such, use of Group (1) does not contradict Watanabe's teachings. Rather, use of Group (1) at the 5' end of a PMO well reflects and is in line with Watanabe's teachings as Watanabe taught "any" one of Group (1), Group (2), and Group (3) is used as the 5' end group and further exemplified actual use of Group (1).

"A known or **obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product** for the same use." *In re Gurley* (27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). (emphasis added).

"**A reference does not teach away, however, if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed.**" *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327, 90 USPQ2d 1865 (Fed. Cir. 2009). (emphasis added).

In view of the foregoing, this rejection is maintained.

Claims 16-17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Popplewell et al. in view of Watanabe et al. for the reasons of record as set forth in the Office action mailed on February 28, 2017 and for the reasons set forth below.

Applicant's arguments filed on August 28, 2017 have been fully considered but they are not persuasive. Applicant argues there is no motivation to select SEQ ID NO:22 as a lead compound for modification. In response, it is noted that there is no *per se* rule that requires a selection of a single lead compound for obviousness under §103. See MPEP §2143: The Federal Circuit in *Eisai* makes it clear that from the perspective of the law of obviousness, **any known compound might possibly serve as a lead compound…**It should be noted that the **lead compound cases do not stand for the proposition that identification of a single lead compound is necessary in every obviousness rejection of a chemical compound**." (emphasis added).

Applicant argues Popplewell's disclosure includes "millions of different possible molecules" thus the "scope" within SEQ ID NOs:1-12 is "vast." In response to applicant's illogical arguments, Popplewell's SEQ ID NO:10 (a 30-mer sequence wherein X can be U or T) that is expressly taught to be amenable to being shortened to a 25-mer, 26-mer, 27-mer, 28-mer, and 29-mer does not encompass applicant's alleged "millions of different possible molecules" even if Popplewell's paragraph 0031 pointed out by applicant is considered, thus the species encompassed by Popplewell's SEQ ID NO:10 is not "vast." Applicant's arguments are so fallible

and incongruent because there is no reason to count the numbers of species for all SEQ ID NOs:1-12 because three nucleotide sequences (SEQ ID NOs:10, 11, and 12) are the only sequences for skipping exon 53. Note that SEQ ID NOs:1-9 do not relate to skipping exon 53. As such, applicant's exaggerated arguments do not support applicant's allegation. The examiner fails to understand why applicant continues to exemplify SEQ ID NO:1 that skips exon 44.

Applicant proposes that one of ordinary skill in the art would rather choose SEQ ID NO:21, which was "superior" to other molecules including SEQ ID NO:22. In response, applicant's proposed idea does not support the alleged nonobviousness of the claims because there is no legal requirement that the selected molecule for modification must be superior to other species in the cited art.

"A known or **obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product** for the same use." *In re Gurley* (27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). (emphasis added).

Further, the mere fact that SEQ ID NO:21 was found superior to SEQ ID NO:22 does not provide any evidence that one of ordinary skill was taught away from making a 25-mer based on SEQ ID NO:22.

Furthermore, applicant's attention is directed to the fact that Popplewell's SEQ ID NO:21 is not targeted to exon 53. SEQ ID NO:21 is designed to skip exon 46. Hence, the examiner fails to understand applicant's argument regarding SEQ ID NO:21.

Applicant then presents another line of reasoning for not selecting SEQ ID NO:22 by pointing out that Watanahe selected SEQ ID NO:21 "from all the possible molecules of Popplewell". In arguing so, applicant points out Watanahe's Table 2 containing 16 PMOs, wherein PMO 12 and PMO 15 correspond to SEQ ID NO:21. Applicant's attention is directed to the fact that there is no disclosure in the Watanabe's publication that SEQ ID NO:21 was indeed selected "from all the possible molecules of Popplewell". Further, as noted above, Popplewell's

SEQ ID NO:21 is for skipping exon 46 thus irrelevant to the instantly claimed subject matter as well as the instant ground of rejection.

For the sake of argument, Popplewell's SEQ ID NO:21 pointed out by applicant will be interpreted as SEQ ID NO:24. Now, applicant's attention is directed to the fact that the Popplewell's NPL (*Neuromuscular Disorders*, 2010) mentioned in the Watanabe's publication and also in applicant's remarks clearly and unambiguously shows that SEQ ID NO:22 targeted to "H53A30/2" ("PMO-H") is more efficient in exon 53 skipping (87.2%) than applicant's proposed selection of SEQ ID NO:24 targeted to "H53A30/1" ("PMO-G") providing 52.4% skipping in normal muscle cells. See Table 1 of the 2010 reference. See also Figure 1 of the 2010 reference demonstrating that there is no significant difference between "H53A30/2" ("PMO-H") and "H53A30/1" ("PMO-G") in exon 53 skipping activity in DMD muscle cells. See also Figure 1 legend: "PMO-G gave significantly higher efficacy of exon skipping than PMOs C, D, E, F, J, K and L ($p<0.005$), **but not significantly higher than PMOs** A, B, **H**, I and M." (emphasis added). Most important, there is no evidential basis that Watanabe purposefully selected "H53A30/1" over "H53A30/2" "from all the possible molecules of Popplewell" because "H53A30/2" is deemed unsuitable or undesirable. There is no teaching-away evidence that a relevant artisan would not have selected Popplewell's SEQ ID NO:22 and make a 25-mer consisting of the instantly claimed sequence. Applicant's attention is also directed to Popplewell's paragraph 0086 expressly disclosing that SEQ ID NO:22 (also referred to as "PMO-H") provided efficient exon 53 skipping in muscle cells such that "at 300 nM, PMO-G and **PMO-H gave over 80% skipping of exon 53** (data not shown)." (emphasis added). See also paragraph 0087 disclosing that PMO-H provided efficient exon 53 skipping in DMD patient muscle cells such that "PMO-G, **PMO-H** and PMO-A were **most active producing in the order of 60% exon skipping** (FIG.8)." (emphasis added). As such, applicant's various attempts to undermine Popplewell's SEQ ID NO:22 are found spurious and unpersuasive.

Applicant asserts that there is no reason to shorten Popplewell's SEQ ID NO:22 because a 25-mer exhibited "poor" exon skipping activity compared to a 30-mer thus Popplewell "teaches away" from making a 25-mer. Contrary to applicant's assertions, there is no express teaching-away disclosure that a 25-mer should not be synthesized. If such were the case, Popplewell would not have claimed at least a 25-mer length of SEQ ID NO:22. In addition, the mere fact that a 25-mer showed a lower level of exon skipping than a 30-mer does not clearly discourage or disparage making a 25-mer PMO. Again, note that "A known or **obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product** for the same use." *In re Gurley* (27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). (emphasis added). Also note that "**A reference does not teach away, however, if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed.**" *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327, 90 USPQ2d 1865 (Fed. Cir. 2009). (emphasis added).

In the instant case, there is no express criticism or discouragement in the Popplewell reference regarding making a 25-mer PMO, even if applicant's assertion that a 30-mer performs better thus Popplewell implicitly expressed "a general preference" for a 30-mer PMO is fully taken into consideration. Again, if Popplewell indeed expressly taught away from making a 25-mer, Popplewell would not have described making a 25-mer in the specification, nor would have claimed a 25-mer PMO in the patent application publication.

In fact, Popplewell synthesized and tested a 25-mer (targeted to positions +35+59) referred to as "PMO-A" that is shortened from SEQ ID NO:22 (positions +33+62). Now, note that Popplewell taught "PMO-A" showed exon skipping activity in normal muscle cells such that "**higher levels of exon skipping were observed for PMO-A** and PMO-B only, with 300 nM doses producing **41.2%** and 34.3% exon skipping, respectively." (emphasis added). See

paragraph 0085. Further, Popplewell taught that PMO-A produced long-lasting exon skipping of over 60% in DMD patient cells. See paragraph 0088: "The exon skipping produced by the six most bioactive PMOs was shown to be persistent, lasting for up to 10 days after transfection, with **over 60% exon skipping observed for the lifetime of the cultures for PMO-A**, PMO-G and PMO-H (FIG. 10a, b). **Exon skipping was shown to persist for 21 days for PMO-A** and PMO-G (FIG. 10c)." (emphasis added). Hence, applicant's spurious arguments addressing non-exon 53 skipping oligonucleotides and variable levels of exon skipping do not whatsoever rebut the objective facts/disclosures regarding the long-lasting, effective exon skipping activity of the 25-mer ("PMO-A") taught, claimed, and disclosed by Popplewell, wherein the 25-mer is designed/truncated from SEQ ID NO:22.

The examiner fails to understand applicant's arguments addressing PMO-B (see pages 25 and 27). Note that the instant rejection is based on the 25-mer sequence targeted to positions +36+60 encompassed by SEQ ID NO:22 (positions +33+62), wherein PMO-A targeted to +35+59 is strikingly similar to the instantly claimed sequence by only 1 nucleotide shift, whereas PMO-B targeted to +38+62 differs from the claimed sequence by 2 nucleotide shift. Now, note that Popplewell expressly taught that "**higher levels of exon skipping were observed for PMO-A and PMO-B only**, with 300 nM doses producing 41.2% and 34.3% exon skipping, respectively." (emphasis added). See paragraph 0085. Further, Popplewell described PMO-A and PMO-B as "the **most bioactive 25mers (PMO-A and PMO-B)**" (emphasis added). See paragraph 0089. As such, Popplewell expressly taught 25-mer POMs designed based on SEQ ID NO:22, wherein the 25-mers have only 1-2 nucleotide shift from the 25-mer rendered obvious in the instant rejection are deemed active in providing exon skipping. As such, applicant's arguments regarding "unpredictable" nature of AONs by addressing non-exon 53 skipping oligonucleotides and the less exon skipping activity by PMO-A and PMO-B compared to 30-mer (e.g., PMO-H; SEQ ID NO:22) are not sufficient to show teaching-away or lack of reasonable

expectation of success. Further, applicant's argument addressing various levels of exon 53 skipping is not sufficient to rebut the instant obviousness rejection because the variability is not the same as unpredictability. In addition, note that "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 [82 USPQ2d 1321] (Fed. Cir. 2007).

Applicant argues one skilled in the art would not have modified the 5' end of Popplewell's PMO by incorporating Watanabe's PEG conjugate. Applicant then suggests her own idea that one skilled in the art would have incorporated Watanabe's Group (2) or Group (3) modification, not the PEG modification. In response, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant argues Popplewell used "Gene Tools LLC", which utilizes Watanabe's Group (2) modification, not the PEG modification and Popplewell does not teach modifying the existing 5' modification. In response, applicant cannot attack a single reference to show nonobviousness of a claimed feature when a combination of references is used to render the claimed feature obvious. That is, applicant cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Now, the fact that Popplewell's PMO did not have the instantly claimed 5'-PEG conjugate is not sufficient to render the instantly claimed 5'-PEG conjugate nonobvious, because Watanabe taught three identified 5' end structures that are suitable to be utilized when making an exon skipping PMO. Since a finite number (only three) of suitable, alternative 5' modifications for an exon skipping PMO were identified and known in the art, a person of ordinary skill in the

art would have reasonably pursued making a 5'-PEG (Watanabe's Group (I)) conjugated PMO as an obvious alternative approach to Popplewell's PMO comprising Watanabe's Group (II), wherein the fact that Popplewell's PMO comprises one of Watanabe's three 5' groups reasonably suggests that Watanabe's three 5' groups were in fact a finite number of art-recognized, alternative 5' groups when making an exon skipping PMO.

In view of the foregoing, this rejection is maintained.

Claims 16-17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sazani et al. in view of Watanabe et al. for the reasons of record as set forth in the Office action mailed on February 28, 2017 and for the reasons set forth below.

Applicant's arguments filed on August 28, 2017 have been fully considered but they are not persuasive. Applicant's repeated "lead compound" argument is not found persuasive. Note that there is no *per se* rule that requires a selection of a single lead compound for obviousness under §103. Applicant argues that one of ordinary skill in the art would be "discouraged" from shortening SEQ ID NO:631 to a 25-mer "based on the teachings of Popplewell discussed above." The examiner fails to understand why Popplewell's teachings are relevant to the instant rejection. Sazani is a completely independent and different from Popplewell, and the instant rejection is not based on Popplewell. Further, there is no teaching in Sazani that refers to Popplewell's '212 publication. Furthermore, even if one should consider Popplewell for the instant rejection, there is no teaching whatsoever in Popplewell that clearly "discourages" one of ordinary skill in the art from making a 25-mer based on the effective 30-mer sequence as amply explained hereinabove. In addition, applicant's attention is directed to the fact that a reference does not teach away unless there is an express discouragement.

"**A reference does not teach away, however, if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise**

discourage investigation into the invention claimed." *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327, 90 USPQ2d 1865 (Fed. Cir. 2009). (emphasis added).

Applicant argues one skilled in the art would utilize Watanabe's Group (3) instead of Group (1). In response, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant argues there is no reasonable expectation of success "for all the reasons already discussed above." If applicant is referring to the arguments addressed in the previous rejections, it is noted that applicant's arguments are not found persuasive for the same reasons set forth hereinabove, which are fully incorporated by reference herein.

In view of the foregoing, this rejection is maintained.

Claims 16-17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wilton et al. in view of Watanabe et al. for the reasons of record as set forth in the Office action mailed on February 28, 2017 and for the reasons set forth below.

Applicant's arguments filed on August 28, 2017 have been fully considered but they are not persuasive. Applicant's repeated "lead compound" argument is not found persuasive. Note that there is no *per se* rule that requires a selection of a single lead compound for obviousness under §103. Applicant provides spurious arguments stating that Watanabe selected Wilton's SEQ ID NO:193, which is a 31-mer. Applicant's attention is directed to the fact that the mere fact that Watanabe included Wilton's SEQ ID NO:193 in Table 2 does not whatsoever teach, let alone suggest, that Wilton's SEQ ID NO:193 cannot be shortened to a 25-mer or that Wilton's SEQ ID NO:193 was prohibited from being truncated to a 25-mer. In addition, applicant's attention is directed to the fact that Watanabe taught making an exon 53 skipping oligonucleotide targeted to

positions +36+60, which are the same positions targeted by the oligonucleotide sequence encompassed by Wilton's claims and by applicant's claims. See the anticipation and obviousness rejections over Watanabe's '062 publication. Applicant's spurious and illogical argument addressing Watanabe's use of the full 31-mer cannot nullify the objective fact that Wilton claimed a 25-mer comprising at least "20 consecutive bases" of SEQ ID NO:193 for exon 53 skipping.

Applicant argues there is no reason to add three bases to arrive at the claimed 25-mer sequence. In response, it is noted that the nucleotide sequence limitation as claimed in Wilton's claims does read on tbe instantly claimed nucleotide sequence. There is no reason/motivation needed in order to arrive at the claimed nucleotide sequence. One of ordinary skill in the art reading and interpreting Wilton's claims would readily understand that the instantly claimed nucleotide sequence reads on Wilton's claimed nucleotide sequences.

Applicant argues one skilled in the art would utilize Watanabe's Group (3) instead of Group (1) and Wilton's SEQ ID NO:193 has Group (3). In response, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Note that applicant did not provide any persuasive rebuttal arguments as to why one skilled in the art would not utilize Watanabe's Group (1) hence failed to properly rebut the instant rejection.

Applicant generally alleges, without any specific, objective evidence, that "there was a significant level of unpredictability associated with selecting specific AONs to induce effective exon skipping of human dystrophin pre-mRNA at the time of the invention." Note that the instantly claimed 25-mer sequence reads on Wilton's claims thus there is no "significant level of unpredictability" regarding the claimed PMO nucleotide sequence.

In view of tbe foregoing, this rejection is maintained.

Double Patenting

Claims 16-17 remain provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-2, 5-35, 39, and 42 of Application No. 15/417,401 for the reasons of record as set forth in the Office action mailed on February 28, 2017 because applicant did not provide any substantially rebuttal arguments.

Claims 16-17 remain provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22, 24, and 27 of Application No. 15/420,823 for the reasons of record as set forth in the Office action mailed on February 28, 2017 because applicant did not provide any substantially rebuttal arguments.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA H SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday-Thursday: 8am - 6:30pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, RAM SHUKLA can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DANA H SHIN/
Primary Examiner, Art Unit 1674

Document Description: Letter Express Abandonment of the application

PTO/AIA/24 (07-17)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

EXPRESS ABANDONMENT UNDER 37 CFR 1.138

File the petition electronically using EFS-Web
Or **Mail** the petition to:
Mail Stop Express Abandonment
Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Application Number	14/776,533
Filing Date	371(c) September 14, 2015
First Named Inventor	Richard K. BESTWICK
Art Unit	1635
Examiner Name	Shin, Dana H.
Attorney Docket Number	4140.0050002

Please **check only one** of boxes 1 or 2 below:
(If no box is checked, this paper will be treated as a request for express abandonment as if box 1 is checked.)

1. ☒ **Express Abandonment**
I request that the above-identified application be expressly abandoned as of the filing date of this paper.

2. ☐ **Express Abandonment in Favor of a Continuing Application**
I request that the above-identified application be expressly abandoned as of the filing date accorded the continuing application filed previously or herewith.

NOTE: A paper requesting express abandonment of an application is not effective unless and until an appropriate USPTO official recognizes and acts on the paper. See the Manual of Patent Examining Procedure (MPEP), section 711.01.

TO AVOID PUBLICATION, USE FORM PTO/AIA/24A INSTEAD OF THIS FORM.

TO REQUEST A REFUND OF SEARCH FEE AND EXCESS CLAIMS FEE (IF ELIGIBLE), USE FORM PTO/AIA/24B INSTEAD OF THIS FORM.

I am the:

☐ applicant.

☒ attorney or agent of record. Attorney or agent registration number is 60,238

☐ attorney or agent acting under 37 CFR 1.34, who is authorized under 37 CFR 1.138(b) because the application is expressly abandoned in favor of a continuing application (box 2 above must be checked). Attorney or agent registration number is _____

/Neil P. Shull, Reg.#60,238/
Signature

March 20, 2019
Date

Neil P. Shull
Typed or printed name

(202) 371-2600
Telephone Number

Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below.

☐ Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.138. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process an application). Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop Express Abandonment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Notice of Abandonment	Application No. 14/776,533	Applicant(s) BESTWICK et al.
	Examiner DANA H SHIN	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

This application is abandoned in view of:

1. ☐ Applicant's failure to timely file a proper reply to the Office letter mailed on _____.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 to the final rejection. (A proper reply under 37 CFR 1.113 to a final rejection consists only of:(1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) if this is utility or plant application, a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. Note that RCEs are not permitted in design applications.)
   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).
   (d) ☐ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $ _____ is insufficient. A balance of $ _____ is due.
   The issue fee required by 37CFR 1.18 is $ _____ . The publication fee, if required by 37 CFR 1.18(d), is $ _____ .
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☑ The letter of express abandonment which is signed by the attorney or agent of record or other party authorized under 37 CFR 1.33 (b). See 37 CFR 1.138(b).

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The reason(s) below:

_____

/DANA H SHIN/
Primary Examiner, Art Unit 1635

Petitions to revive under 37 CFR 1.137, or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.

EXHIBIT C

THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (GBW) [redacted]
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC. Plaintiff/Counter-Defendants.	

REPLY EXPERT REPORT OF STEVEN F. DOWDY, Ph.D.

[redacted]

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I, Steven F. Dowdy, Ph.D., declare as follows:

I. INTRODUCTION

1. I have been retained by counsel for Defendant/Counter-Plaintiffs Sarepta Therapeutics, Inc. ("Sarepta") and the University of Western Australia ("UWA") as an independent expert in the above captioned matter. I submitted an Opening Expert Report ("Dowdy Op. Rep.") on (1) the infringement of U.S. Patent Nos. 9,994,851 ("the '851 Patent"); 10,227,590 ("the '590 Patent"); and 10,266,827 ("the '827 Patent") (collectively, "the Wilton Patents"); (2) the invalidity of U.S. Patent Nos. 9,708,361 ("the '361 Patent); 10,385,092 ("the '092 Patent"); 10,407,461 ("the '461 Patent"); 10,487,106 ("the '106 Patent"); 10,647,741 ("the '741 Patent"); 10,662,217 ("the '217 Patent"); and 10,683,322 ("the '322 Patent") (collectively, "the NS Patents"); and (3) the materiality of certain withheld information and affirmative misrepresentations made with respect to the NS Patents. I also submitted a Rebuttal Expert Report ("Dowdy Reb. Rep.") on the validity of the Wilton Patents and responded to certain arguments raised by NS's experts Drs. Hastings, Kamholz, Wood, and Esau.

2. A copy of my curriculum vitae was provided as Appendix A to my Opening Expert Report. The information regarding my credentials and qualifications, compensation, and testifying experience with the last four years was also provided in my Opening Expert Report, Sections I-II. My Opening Expert Report is incorporated by reference in its entirety. My Rebuttal Expert Report is also incorporated by reference in its entirety.

3. As explained in detail below, I submit this Reply Expert Report in response to arguments presented by: (1) Christine C. Esau, Ph.D. in her Rebuttal Expert Report Regarding Non-Infringement of the Wilton Patents ("Esau Reb. Rep."); (2) Dr. Michelle L. Hastings in her Responsive Expert Report Regarding the Validity of the NS Patents ("Hastings Resp. Rep."); and (3) Dr. Matthew J.A. Wood in his Rebuttal Expert Report ("Wood Reb. Rep."); all of which I

prosecution of the NS Patents. For the reasons discussed above and in my Opening Report, it is not. *See supra* § VI.B.1; Dowdy Op. Rep. § XI.C.

183. Second, Dr. Hastings is again commenting on Sarepta's state of mind, which I understand is improper for an expert. *See, e.g.*, Dowdy Op. Rep. ¶56.

184. Third, even assuming it is somehow relevant, one cannot make any conclusions about the alleged cumulativeness of Sazani 2010 based on these Sarepta applications without considering the prior art references submitted in those cases—which Dr. Hastings did not do. Notably, the abandoned '533 Application and Passini US '600 have priority dates that are *later in time* than the effective filing date for the NS Patents, meaning that the universe of available prior art is necessarily different. Specifically, the '533 Application claims priority to Bestwick PCT '240, which in turn claims priority to a provisional application filed in March 2013. *See* Bestwick PCT '240, item (30). Thus, the earliest possible priority date for Bestwick PCT '240 is about 1.5 years *after* the August 31, 2011 effective filing date of the NS Patents. Passini US '600 claims priority to a provisional application filed in December 2016, which is more than 5 years *after* the effective filing date of the NS Patents. Passini US '600, item (60). Because the patents involve different priority dates and different cited references, Dr. Hastings' failure to analyze the art considered in the Sarepta patent applications negates her speculation about what Sarepta might have thought about the cumulativeness of Sazani 2010.

VII. THE WILTON PATENTS ARE NOT INVALID

185. In my Rebuttal Expert Report, I opined that the Wilton Patents satisfy the written description requirement. *See* Dowdy Reb. Rep. § V.A. I also responded to several arguments raised by Dr. Hastings, including her improper dismissal of the hot spot of exon 53 that Dr. Wilton and co-inventors identified as of June 2005. *See id.* § V.A.4.a. In her rebuttal expert report, Dr. Hastings attempts to support her positions with "[a]dditional post-priority date evidence" identified

DATE: Oct 27, 2023 By: _____

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